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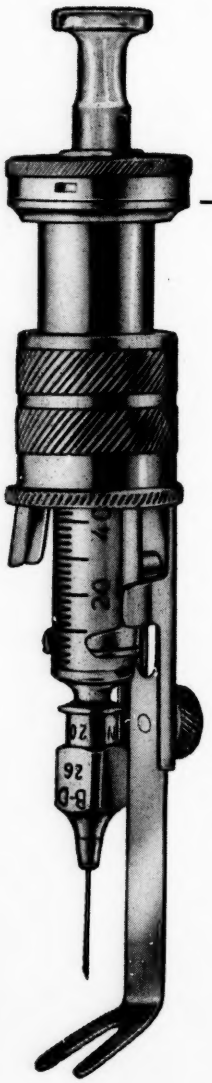

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POTASSIUM
In the Treatment of Diabetic Coma

Joseph H. Crampton, M.D.
George W. Mellinger, M.D.
Lester J. Palmer, M.D.
SEATTLE, WASHINGTON

Emphasis on early and adequate use of insulin and fluid therapy and the introduction of antibiotics have resulted in a marked reduction in the mortality from diabetic coma during recent years.[1, 2] Hope for further decrease has been stimulated by the demonstration of profound alterations in potassium metabolism and the response of these changes to appropriate therapy.

POTASSIUM METABOLISM IN ACIDOSIS

Atcheley and others[3] first demonstrated a markedly negative potassium and phosphorus balance during the development of diabetic coma with a corresponding positive balance during recovery. Holler[4] proved the clinical significance of potassium in diabetic coma in a patient who developed severe dyspnea due to almost complete paralysis of the respiratory muscles 21 hours after the initiation of therapy. The concentration of serum potassium was 2.5 mEq./L.; potassium chloride given intravenously produced a prompt and dramatic improvement. It was immediately suspected[5] that in many cases death attributed to respiratory failure or vascular collapse after apparent recovery from acidosis may have been, in fact, caused by hypopotassemia. That this suspicion was well-founded has been adequately proved.[5–7]

During diabetic acidosis, first there is increased glycogenolysis and gluconeogenesis resulting in a marked shift of potassium and phosphorus from the intracellular space; secondly, there is profound diuresis which washes out the intracellular ions thus mobilized; and thirdly, there may be terminal dehydration with contraction of the intracellular and extracellular spaces resulting in oliguria, prerenal azotemia and hyperpotassemia.[3, 8] A paradoxical condition of elevation of serum potassium and phosphorus despite a total body depletion of these elements is produced.[8–12]

During therapy, on the other hand, there are 1) rehydration with expansion of the extracellular space and resulting dilution of potassium; 2) re-establishment of urinary excretion with further loss of potassium; and 3) the movement of potassium into cells during glycogen storage and cellular rehydration. A moderate to marked fall in serum potassium results during the treatment of diabetic coma.[8–12] The fall in serum potassium, although significant, is not usually of a degree sufficient to produce untoward effects; nevertheless, the numerous demonstrated examples of morbidity or death due to hypopotassemia make mandatory the consideration of this possibility in all cases of diabetic coma.

From the Mason Clinic. Address communications to Dr. Crampton, 1115 Terry Avenue, Seattle 1, Washington.

Presented at the Twelfth Annual Meeting of the American Diabetes Association, Chicago, June 8, 1952.

HYPOPOTASSEMIA

Symptoms of hypopotassemia encountered in the treatment of diabetic coma include: varying degrees of skeletal muscle paralysis with or without associated respiratory distress,[4, 5] vascular collapse[13] which responds to intravenous infusion of a solution containing potassium but not to blood transfusion, and intestinal ileus with increasing nausea and vomiting (see below).

Opinion varies as to the best method of prevention and treatment of hypopotassemia. Some authors[2, 14] feel that infusion of fluids containing potassium in low concentration should be stated routinely three to six hours after institution of therapy, providing the urinary output is adequate. Others[15] think that the requirements for potassium usually can be satisfied with early oral feedings if the initial dosage of insulin has been adequate, and if no intravenous glucose has been given early in therapy. The latter observers have reserved oral or intravenous potassium for the treatment of symptoms of hypopotassemia. We believe that prevention of hypopotassemia is more logical than treatment after symptoms have occurred. Since potassium can be given orally with safety in the presence of an adequate urinary excretion, we have administered it routinely except in mild cases. Such therapy prevents clinically significant hypopotassemia in virtually all instances; it obviates the necessity for determination of serum potassium in the majority of cases.

In the event of inability of the patient to ingest potassium, or if symptoms of hypopotassemia appear, additional potassium may be used intravenously. Study of the serum potassium with the flame photometer becomes valuable if the patient is not responding to therapy properly. In any case with vascular collapse and oliguria, the use of potassium intravenously would be hazardous in the absence of serum potassium determination.

PLAN OF TREATMENT

The patient is given an initial dose of insulin which must be based entirely on clinical evaluation. In adults this varies from 100 to 300 units. As soon as the blood sugar is determined, the initial dose is supplemented so that the total amount of insulin given in the first one or two hours in units is equal to half the admission value for blood sugar (Table I). These dosages are reduced in the young, the aged, or in any instance where insulin sensitivity is recognized or suspected. They are increased in the presence of known insulin resistance. We do not hesitate to give all or part of these amounts of insulin intravenously if vascular collapse is present or impending. Insulin is used in regular or crystalline form only during the first twenty-four hours.

TABLE I. Total Amount of Insulin Given in the First Two Hours

ADMISSION BLOOD SUGAR, mg. per 100 cc.	INSULIN DURING FIRST 2 HRS., UNITS
300	150
400	200
500	250
600	300
700	350
800	400
900	450
1000	500

After the initial dose of insulin is administered, the other measures usually advocated in the treatment of diabetic coma are carried out. At first fluids are given intravenously in the form of physiological saline only. Glucose is never given until there has been demonstrated an adequate fall in blood sugar, or until the urine has become sugar free. Intravenous treatment with lactate is not given; sodium bicarbonate is used only in rare instances.

An indwelling catheter is always inserted into the bladder. One can then ascertain merely by a glance whether or not the urinary output is adequate.

After a period of four hours has elapsed, the contents of the stomach are aspirated; 80 cc. of 10 per cent solution of dibasic potassium phosphate diluted in 100 cc. of water are instilled into the stomach. This treatment is given only if it can be domonstrated that the rate of flow of urine from the catheter is adequate. The rate of flow (number of drops per minute) from the catheter should be approximately one-half that of the intravenous saline.

As soon thereafter as the patient is able to take fluids without nausea, he is given hourly feedings of 100 gm. of fruit juice, broth or milk, to which 10 to 20 cc. of dibasic potassium phosphate have been added. This regimen is usually continued for four to six hours.

The level of blood sugar and the carbon dioxide combining power of the plasma (and more recently the serum potassium) are determined at intervals of four hours until return to normal can be demonstrated. If the drop in the blood sugar at the fourth hour is not satisfactory, the initial dose of insulin is repeated in equal or increased amounts.

Intravenous treatment with potassium (in the form of one per cent potassium chloride in the water) is given only if: 1) the patient is unable to take potassium phosphate by mouth, 2) the urinary output is

adequate, 3) there is hypopotassemia as evidenced by vascular collapse, muscular weakness, respiratory distress, or actual measurement.

We have found it necessary to give intravenous potassium in only five instances.

RESULTS

In order to compare our results in the treatment of diabetic coma before and after the inauguration of supplemental potassium therapy in June, 1948, we have carefully reviewed all instances of coma treated by us over a ten year period. All cases of diabetic coma in which the carbon dioxide combining power was less than 10 mEq. are included. The group treated since the use of potassium was started included 11 cases with less serious coma in which food could be taken early and in which there was rapid improvement on therapy without potassium. These cases were not considered separately.

As will be seen in Table 2, the patients treated before and after potassium therapy form roughly comparable groups; the only significant difference being the longer duration of diabetes in the cases treated since the use of potassium was begun.

TABLE 2. Comparison of Cases Treated Before and After Potassium Therapy

	32 Cases Before Potassium Therapy		53 Cases After Potassium Therapy	
	Range	Mean	Range	Mean
Age in Years	3-72	30.8	5-65	31.5
Known duration of Diabetes in years	0-17	4.8	0-27	8.0
Admission Blood Sugar, mg. per 100 cc.	273-1396	592	203-1048	546
Admission Plasma CO_2, mEq/L	4.1-10	7.0	2.7-10	6.3

TABLE 3. Comparison of Insulin Dosage, Fluid Administration and Time Until Urine Free of Diacetic Acid, Before and After Potassium Therapy

	32 Cases Before Use of Potassium		53 Cases Since Use of Potassium	
	Range	Mean	Range	Mean
Insulin Dosage in two hours, units	28-380*	180*	10-700	237
Insulin Dosage in 24 hours, units	80-710*	355*	63-1090	445
Parenteral fluids given in 24 hrs., liters	1-7	4.1	0.5-10.8	5.2
Hours until diacetic acid absent from urine	5.5-21	11.1	2-31	11.3

*Eliminated from these figures is one case with extraordinary insulin resistance in which 440 units of insulin were given in the first 2 hours and 5,490 units within 24 hours after the onset of coma.

Table 3 shows that the administration of fluids and insulin has increased somewhat in the passing years. The average patient now receives almost 500 units of insulin within the first twenty-four hours after admission, and, nearly all of this is given within four to five hours after admission to hospital. It is interesting to note that in spite of the use of larger doses of insulin and increased amounts of fluids, the number of hours required for the disappearance of ketonuria is almost exactly the same in the two groups.

Table 4 shows the amount of potassium given in the 42 cases given this treatment. It will be noted that some patients received as high as 48 gm. of dibasic potassium phosphate (551 mEq. of K.). The average amount administered was 18.6 gm. (214 mEq. of K.).

TABLE 4. Summary of Potassium Administered in 42 Cases

	Range	Mean
Grams K_2HPO_4 Given	4-48	18.6
mEq. K^+ Given	46-551	214
Hours before potassium started	1-12	5.1

After starting this plan of therapy, we had the good fortune to obtain a Weichselbaum-Varney flame photometer. Serial determinations of serum potassium with this instrument have given further proof of the profound changes in serum potassium and of the efficacy of this new plan of therapy.

ILLUSTRATIVE CASE HISTORIES

CASE 1. An eight-year-old, white boy without previous history of diabetes was semistuporous on admission. The level of blood sugar (Figure 1) was 432 mg. per

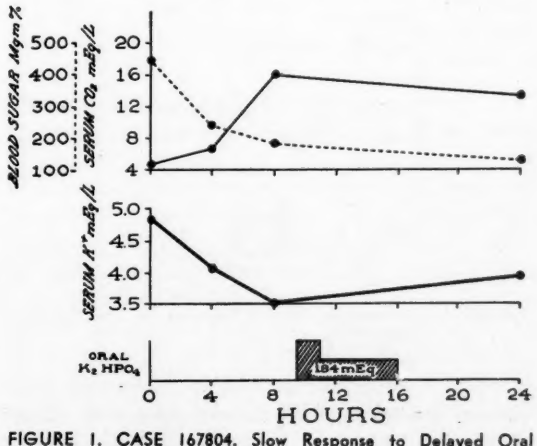

FIGURE 1. CASE 167804. Slow Response to Delayed Oral Potassium Therapy

100 cc. and the carbon dioxide combining power 4.7 mEq. He responded satisfactorily to treatment with 50 units of crystalline insulin and saline given intravenously; the test for diacetic acid in the urine became negative in 11 hours. The serum potassium was 4.7 mEq. on admission and fell to 3.5 mEq. in 8 hours. A total of 16 gm. of dibasic potassium phosphate (184 mEq. of K.) was given by mouth beginning nine and one-half hours after admission. The serum potassium concentration rose to 3.9 mEq. at the twenty-fourth hour. No symptoms due to hypopotassemia were noted.

CASE 2. A white man, aged 21 years, who had known diabetes for 14 years was admitted with moderate dyspnea and an odor of acetone on his breath. The blood sugar was 604 and the carbon dioxide combining power 9.4 mEq. (Figure 2). The response to an initial dose of 200 units of insulin and intravenous infusion of fluids was satisfactory. No further difficulties were encountered. The serum potassium was 6.2 mEq. on admission and fell to 4.3 mEq. in four hours. Twenty gm. of dibasic potassium phosphate (230 mEq.) were given by mouth beginning at the fourth hour. It is seen that the serum potassium concentration rose as a result, and that a normal serum potassium was maintained.

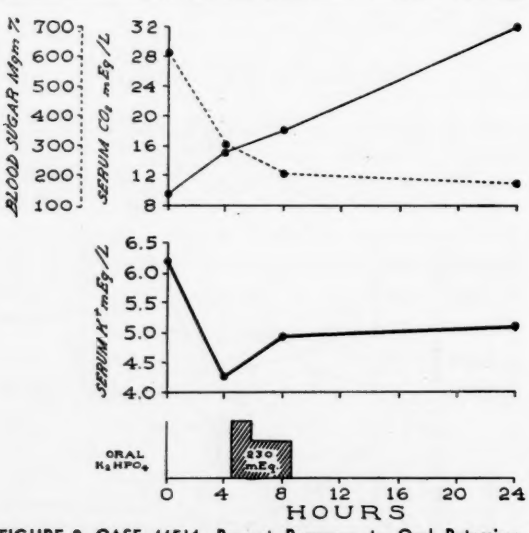

FIGURE 2. CASE 66514. Prompt Response to Oral Potassium Therapy

CASE 3. A white woman with a 13-year history of diabetes was admitted in diabetic coma with marked dehydration, Kussmaul respiration and an odor of acetone on her breath. The blood sugar was 448 and the carbon dioxide combining power 4.8 mEq., (Figure 3). A total of 250 units of crystalline insulin was given during the first two hours, and 6,500 cc. of fluid were given intravenously during the first 24 hours. The response to therapy was satisfactory; ketonuria disappeared in 8 hours. Oral treatment with potassium was started at the fourth hour; however, nausea began to recur at the sixth hour, and made it necessary to discontinue attempts to give oral feedings and potassium two hours later. The nausea subsided somewhat after the subcutaneous administration of atropine. Oral treatment with potassium and fluids was resumed at the 14th hour; however, the nausea began to increase. At this time the result of the determination of serum potassium at the eighth hour became available; it was 2.9 mEq. Since ketonuria had been absent for six hours, it was thought that the increasing nausea might be a symptom of the hypopotassemia. Potassium was administered intravenously using a solution containing 0.4 per cent potassium chloride and 5 per cent glucose. The nausea disappeared in 15 to 30 minutes and the subsequent course was uneventful. This was the only case in the series in which there were symptoms apparently related to hypopotassemia.

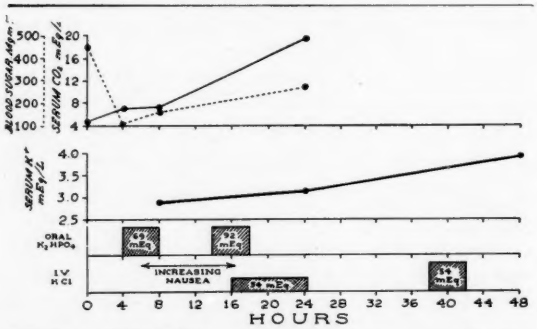

FIGURE 3. CASE 148831. Supplemental Intravenous Potassium Therapy Necessary Because of Nausea

COMMENT

Cases 1 and 2 both demonstrated a satisfactory rise in the serum concentration of potassium following oral potassium. Case 2, in contrast to Case 1, illustrates the importance of beginning the treatment with potassium early; it should usually be started at the fourth hour in order to prevent an abnormally low serum potassium level. Case 3, is an example of the occasional case in which there is not sufficient absorption of potassium from the intestinal tract and supplementary potassium must be given intravenously.

Final proof of the efficacy of any plan of therapy of diabetic coma must lie in the number of patients surviving the episode. That our plan of therapy is efficacious, we believe is shown in Table 5. No fatalities were encountered in a series of 53 cases of coma when the treatment included the use of potassium as compared with 3 deaths in the series of 32 cases treated before the use of potassium.

TABLE 5. Mortality Before and After Use of Potassium in Treatment of Coma

	Patients Before Use of Potassium	Patients After Use of Potassium
Number of Patients	32	53
Deaths due to coma	3	0
Percentage mortality	9.4%	0.0%

We will be the first to admit that there are a number of factors in this achievement, not the least of which are an awareness of the problem and a will to attain the ideal. However, we do feel that the free use of potassium salts has been a significant factor in the absence of mortality reported here.

SUMMARY

In this treatment of diabetic coma, up to 700 or more units of insulin are given during the first two hours; the dose determined by clinical evaluation of the case and the initial blood sugar level. Rehydration is accomplished with saline solution given intravenously.

Additional insulin is given at the fourth hour if the blood sugar has not fallen to one-half of the original level.

If the urinary output is adequate, dibasic potassium phosphate is given by stomach tube and in fluids given orally beginning at the fourth hour. Potassium is given intravenously only if the patient is unable to retain it when given by mouth or if symptoms of hypopotassemia occur.

No fatalities were encountered in a total of 53 cases of diabetic coma so treated in contrast to three deaths in a similar group of 32 cases treated prior to the oral use of potassium.

We believe that our series of 53 consecutive instances of diabetic coma without a death demonstrates the efficacy of the plan of treatment described.

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DISCUSSION

DR. CLIFFORD F. GASTINEAU, (*Rochester, Minn.*): Dr. Crampton has presented an enviable record: no deaths in 53 cases of diabetic coma. It is difficult, by the use of mortality rates, to evaluate the efficacy of potassium in this study, since the mortality rate of 9.4 per cent among the patients who received no potassium is itself an excellent record. Moreover, as Dr. Crampton has pointed out, other factors, such as the amounts of insulin and fluids administered, were different in the two series. Nevertheless, this report is important because it presents a scheme by means of which potassium can be administered safely and in quantities that will correct hypopotassemia.

I was particularly interested in Dr. Crampton's third case, in which he observed nausea associated with hypopotassemia, and found that there was a response to intravenously, but not to orally, administered potassium. The observation that gastrointestinal absorption of potassium occasionally may be inadequate in diabetic acidosis is a valuable one.

In view of the current interest in potassium metabolism, it is surprising how seldom we observe symptoms in the treatment of diabetic acidosis which may be attributed to hypopotassemia. Our arguments for the use of potassium would be weakened if we expected only to prevent the symptoms of hypopotassemia. It seems likely that much more is accomplished by the use of potassium in the treatment of diabetic acidosis than just the prevention of the symptoms of hypopotassemia. It is reasonable to presume that significant deficiencies of potassium and phosphate may occur without manifesting any symptom by which they may be identified, and it is probable that such deficiencies cause a general interference with cellular metabolism, thereby increasing the possibility of a fatal outcome. These presumptions, and Dr. Crampton's demonstration that potassium and phosphate can be administered safely and easily, seem ample justication for the use of these ions in the treatment of diabetic acidosis.

DR. FRED W. S. MODERN (*Long Beach, Cal.*): On my service at the Los Angeles General Hospital, we administer potassium chloride routinely in all cases of diabetic coma in which there is normal urinary excretion. The dosage is 3 gm., given 4 hours, 8 hours and 24 hours after starting treatment.

The first dose is routinely given intravenously, the second and third doses intravenously or orally, depending on the patient's state of consciousness.

The serum potassium is determined before the 4-hour and sometimes before the 8-hour and 24-hour doses. We find the electrocardiogram to be a poor index of hyperpotassemia or hypopotassemia—normal electrocardiograms with the serum potassium as low as 2 mEq. have been found.

We observed two cases of potassium resistance in which death occurred with hypopotassemia despite the administration of large amounts of potassium (close to 20 grams). In both of these cases there was pancreatitis. One patient had coma as the first symptom of his diabetes. As far as we could ascertain, the onset of coma was simultaneous with the onset of the pancreatitis. He died with a blood potassium level of 2 mg. in spite of the fact that within the 20 hours before death he had received about 18 gm. of potassium chloride.

DR. DAVID ADLERSBERG (*New York*): I was particularly interested in the observations of Dr. Crampton concerning the relationship between nausea and hypopotassemia. Another instance of nausea related to hypopotassemia has been recently reported in connection with intolerance to digitalis.

In metabolic balance studies it was found that early symptoms of digitalis intoxication were associated with negative potassium balance and hypopotassemia and that the tolerance of these persons to digitalis was decidedly increased by administration of potassium salts.

I would like to ask whether Dr. Crampton can offer an explanation for the impaired intestinal absorption of potassium salts in diabetic acidosis.

DR. JOSEPH H. CRAMPTON (*closing*): A comment is in order about the phosphate these patients were given. Just as there is a striking fall in the serum potassium with therapy, so is there a similar decline in the serum phosphorus. The oral administration of potassium phosphate rather than potassium chloride helps to compensate for both deficits. However, in spite of the oral administration of phosphate, there still is a marked decline in serum phosphate. This has been the experience of Franks et al who gave large amounts of phosphate intravenously.

I believe changes in the electrocardiogram are an extraordinarily poor index of the serum potassium. It has been postulated that they are an index of changes in cellular potassium. Having had difficulty with hypopotassemia in only one instance, we are not in a position to evaluate this point. However, it is our impression that many of the inconsistencies originally noted in this field may have been the result of technical difficulties in potassium determinations with the flame photometer.

With regard to the question as to impaired intestinal absorption, I have no direct explanation for the impairment except to say that the absorption is related to serum electrolyte concentration. In our instance, the explanation is simple. The patient was unable to retain any potassium by mouth, therefore none was absorbed.

THE HOUSSAY PHENOMENON IN MAN

Recovery from Retinopathy in a Case of Diabetes With Simmonds' Disease

Jacob E. Poulsen, M.D. GENTOFTE, DENMARK

In a rare but instructive combination of endocrine disorders, nature has made the Houssay experiment in the human being. This has been observed in a small number of cases of diabetes, when damage to the pituitary gland by disease has caused loss of pituitary function with resultant modification of the diabetes. The changes in the ocular complications of diabetes observed in the following case are of special interest.

CASE REPORT

A female patient, born in 1915, had diabetes which began in 1924. During childhood and early youth it was very difficult to keep her diabetes under control; she was careless and uncooperative in regard to treatment. She had coma at least 20 times and was admitted to almost all the hospitals in Copenhagen. From 1936 to 1939, she was admitted 11 times to Steno Memorial Hospital, on each occasion with ketosis and often with infectious complications.[12]

During one of the hospital visits, the basal metabolism was found to be decreased; she was then periodically treated with thyroid preparations in variable doses.

Read, with modifications, at the Congress of the International Diabetes Federation, Leyden, Netherlands, July, 1952.

Address communications to Dr. Poulsen, Niels Steensens Hospital, Gentofte, Denmark.

In 1949, the patient's condition was observed again, in the course of a follow-up study of our juvenile cases of diabetes. The case record was brought up to date. She said that menstruation had occurred regularly from her sixteenth year. In 1944 she had a miscarriage in the third month of pregnancy, and in early 1945 a second miscarriage in the fourth month. She became pregnant for the third time in March 1945.

For years prior to this pregnancy the insulin dosage had been from 80 to 100 units daily, reaching 120 units in February and March 1945. During the pregnancy the insulin requirement was lessened; during October and November of the same year, she received about 40 units daily. The pregnancy terminated with the delivery of a dead fetus weighing 2.5 kg. on December 10, 1945.

Just before delivery she had acidosis. Her blood sugar was 400 mg. per 100 cc. and the plasma bicarbonate was reduced to 14 mEq. On December 10, she was given 144 units of insulin in five doses. In the days following, she was given approximately 24 units daily. She had a temporary postpartum psychosis and was transferred to the psychiatric department. While here, on December 19, a severe hemorrhage occurred so that a blood transfusion was required. In the middle of January 1945, she was discharged from the hospital

with an adopted child. The insulin dose was 20 units in the morning, plus 10 units in the evening.

After the delivery there was no engorgement of the breasts. Later she had continued amenorrhea. She also said that she had loss of libido. Soon after the delivery, she began to show sensitivity to insulin; in the succeeding months she had frequent severe hypoglycemic shocks, with unconsciousness requiring admission to hospitals. She reduced the dose of insulin to 8 to 12 units every second and third day.

During the succeeding years she felt weak and tired, but she did not lose weight. It was difficult for her to attend to her duties and take care of her home and baby. She observed that her skin became dry; axillary and pubic hair fell out, and her eyebrows disappeared. She complained of feeling cold, even in temperature pleasant to her family, and she had a tendency to faint with change from horizontal to upright position.

Beginning in 1944, for a year before her postpartum hemorrhage, she complained of diminished vision. She was nevertheless able to read, to sew, and enjoy movies. In October 1945, the sixth month of her pregnancy, she was examined in the University Hospital eye clinic by an expert ophthalmologist (Ronne). He found posterior cortical cataracts and diabetic retinopathy in both eyes. In the eyegrounds, there were scattered hemorrhages formed as points, spots, and stripes, predominantly localized to the small vessels. The hemorrhages were more abundant about the periphery than about the macular region. The patient was reexamined in Steno Memorial Hospital in June 1949, three and a half years after her postpartum hemorrhage. At this time she had only a few hemorrhages (Ballantyne) and a few spotty exudates.

She has been admitted four times since March 1951. The physical examination showed a rather pale, emotionally dull patient without initiative. The skin of her face was wrinkled; there was no pigmentation of the skin or in the mouth. Eyebrows were lacking; axillary hair was absent and pubic hair very scarce. No goiter was palpable. The breasts were rather small. There was atrophy and paleness of the vagina; the uterus was small and hyperinvoluted. Her height was 161.5 cm. and her weight approximately 66 kg. The blood pressure when lying down was 95/60 and when in an upright position 75/60. (Figure 1.)

The routine blood tests (including the sedimentation rate and Wassermann reaction) were normal. The serum cholesterol on August 25, 1951 was 206 mg. per 100 cc., the free cholesterol 59. The serum potassium, sodium, phosphorous, calcium, and chloride values

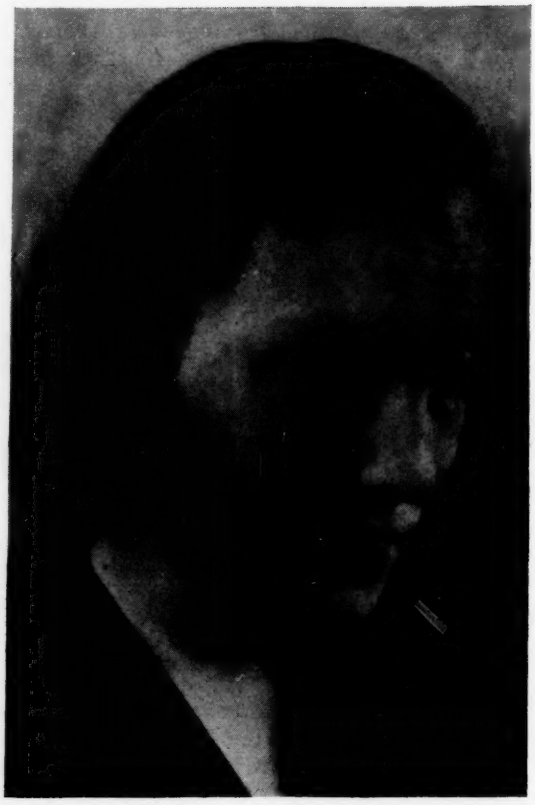
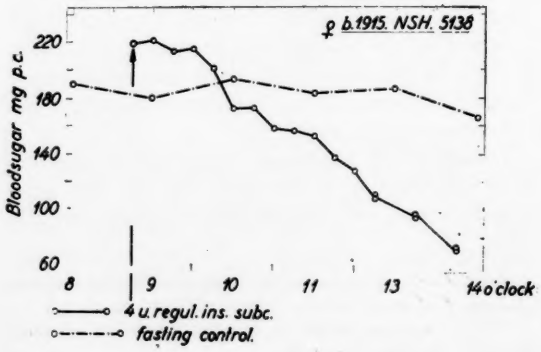


FIGURE 1. Photograph of the patient after recovery from retinopathy, 1951.

FIGURE 2. Test for insulin sensitivity, showing fall in blood sugar from 220 to 73 in four hours.



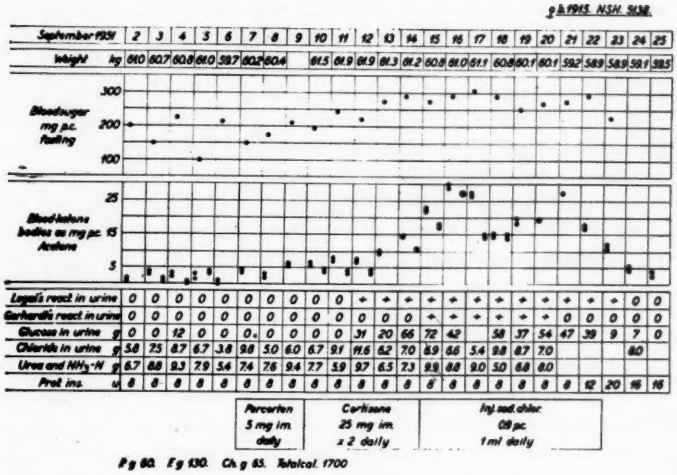

September 1951
Weight kg
Bloodsugar mg p.c. Fasting
Blood-ketone bodies as mg p.c. Acetone
Legal's react. in urine
Gerhardt's react. in urine
Glucose in urine g
Chloride in urine g
Urea and NH3-N g
Prot. ins. u
Percorten 5 mg im. daily
Cortisone 25 mg im. x 2 daily
Inj. sod. chlor. 0.9 p.c. 1 ml daily
P g 80. F g 130. Ch g 65. Totalcal. 1700
Sod. chlor. ab. 5 g daily + diet ab. 9 g

FIGURE 3. Test showing absence of ketone bodies while on ketogenic diet.

were within normal ranges. The Robinson-Kepler-Power water test of the adrenal function showed delayed excretion. The Thorn modification was reported A-15. The urinary excretion of 17-ketosteroids was 6.4 mg. per day in August 1951, 2.9 in May 1952; glucocorticoids 0.36 mg. The eosinophil count after administration of 10 mg. of ACTH in 1952 dropped from 200 to 150. After injection of 0.3 mg. of epinephrine, it dropped from 165 to 106. The control eosinophil counts were 225 and 200. A test for insulin sensitivity (4 units injected subcutaneously) showed a fall in the blood sugar from 220 to 73 in 4 hours (Hagedorn-Jensen blood sugar method). (Figure 2) The urinalysis for albumen was negative; there were no ketone bodies. The x-rays of the sella turcica showed nothing abnormal.

An ophthalmological examination in March 1951 (five years after the postpartum hemorrhage) made by Prof. Ehlers at the eye clinic in the University Hospital showed the cataracts as described previously, but there were now no hemorrhages and no exudates. Repeated examination has confirmed the absence of retinopathy.

The patient was treated with a diet providing approximately 1700 calories and 8 units of protamine insulin. The urine seldom contained sugar. Now and then mild hypoglycemic reactions occurred.

After delivery, ketone bodies were never found in the urine. Special studies were undertaken to observe the ability to produce ketone bodies. (Figure 3) She was placed on a ketogenic diet for a trial period, and still failed to show the appearance of ketone bodies in the urine for five days and even when 5 mg. desoxycorticos-

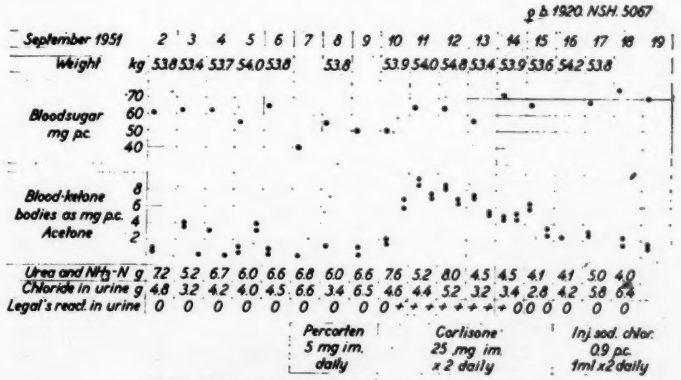

September 1951
Weight kg
Bloodsugar mg p.c.
Blood-ketone bodies as mg p.c. Acetone
Urea and NH3-N g
Chloride in urine g
Legal's react. in urine
Percorten 5 mg im. daily
Cortisone 25 mg im. x 2 daily
Inj. sod. chlor. 0.9 p.c. 1 ml x 2 daily
P g. 50 F g. ab. 125 Ch g 65 Totalcal. ab. 1500
Sod. chlor. ab. 3 g daily + diet ab. 7 g

FIGURE 4. Test as in Figure 3 on nondiabetic subject with Simmonds' Disease.

terone daily was injected the following three days. She was given 25 mg. cortisone twice daily; ketosis then appeared up to a blood-ketone value of 25 mg. per 100 cc. given as acetone. She also showed hyperglycemia and glycosuria without a rise in the excretion of urea. Similar examinations were carried out in a case of Simmonds' disease without diabetes and similar results, in regard to the ketosis, were observed. The investigation confirms the important role of corticosteroids in the production of ketones in diabetics. (Figure 4)

REVIEW OF PREVIOUS REPORTS

I shall very briefly mention the earlier reports concerning diabetes mellitus complicated by hypopituitarism. I have been able to find only eight cases published.

The first case was reported by Lyall and Inness[1] in 1935. The patient was a 29 year old man who had diabetes for two years treated with 80 units of insulin daily. A pathological process in the region of the sella turcica was demonstrated, though the nature of the process was unknown. The insulin requirement decreased and the treatment was finally stopped, without the appearance of sugar in the urine. There was no spontaneous hypoglycemia.

In 1940, Kotte and Vonderahe[2] reported the case of a 40 year old man who had diabetes of 5 years duration requiring insulin in variable doses. He was admitted to the hospital unconscious, pale and sweating. He died 18 hours later. The blood sugar was 31 and 20 mg. per 100 cc. The autopsy showed necrosis of the anterior pituitary gland and also disseminated pulmonary tuberculosis.

Feldman, Roberts, Susselman and Lipetz[3] described the case of diabetes in a 50 year old woman. She had a thyroidectomy for hyperthyroidism at the age of 21 and she had had diabetes from the age of 38, treated with insulin starting with a dosage of 20 to 30 units a day. For two or three years before admission, no insulin was needed and in the last year the urine was constantly free from sugar. One month before admission she suffered from headache, nausea, and weakness. The day before admission she was mentally disturbed, weak, and sweating. Her blood sugar was found to be 35 mg. per 100 cc.; blood pressure 75/30. She died in hypoglycemia. At autopsy, it was found that she had necrosis of about 80 per cent of the anterior pituitary gland. The adrenals were atrophic.

The fourth case was published by Vandenbroeck and Ferin.[4] A female, diabetic since her twenty-eighth year, and treated with 26 to 34 units of insulin, had a miscarriage in the sixth month at the age of 33. The breasts did not become engorged, and menstruation did not return. Afterwards there was a decrease in the insulin requirement to 18 to 25 units. The patient was treated elsewhere later on, but the authors learned that she died in hypoglycemia at the age of 35 years.

Bastenie[5] reported a case of a 41 year old female patient with acromegaly who showed a typical diabetic glucose tolerance curve and fasting hyperglycemia (blood sugar 260 to 300 mg. per 100 cc.) After an acute illness with signs of elevated intracranial pressure and thrombosis of the cavernous sinus, the glycosuria disappeared and the glucose tolerance test became normal.

Marzullo and Handelsman[6] reported the case of a 51 year old man who was found to have diabetes in 1942 when he showed polyuria, loss in weight and blurred vision. The fasting blood sugar was 260 mg. per 100 cc; the blood pressure, 200/90. Examination of the eyes revealed white spotty exudates scattered throughout each fundus, and small linear hemorrhages. He was treated with 40 units of insulin daily. About 3 months later, he was treated for pneumonia. Following discharge from the hospital, his appetite disappeared and he felt weak; the insulin dosage was markedly reduced before the last admission. His fasting blood sugar was 88 mg. per 100 cc., later 64-66 mg. despite discontinuance of insulin treatment the last 25 days, he was alive. Ketonuria did not occur, even during starvation, the blood pressure was 100/70, later 80/60. He was weak, drowsy and without appetite, and expired in coma. During his last stay at the hospital, the ophthalmological examination revealed that cataracts had developed so that studies of the fundi were impossible. It was unfortunate that the outcome in regard to the retinopathy could not be observed. The autopsy showed pituitary necrosis, atrophy of the testes and pneumonia.

The seventh case was reported this year by F. W. Williams.[7] The patient was a woman, 27 years of age in 1934, when her diabetes was discovered. She was treated with diet and insulin, 12 units in 1944 and 60 in 1948. In November 1948 she became pregnant. In February 1949, she suffered from several typical insulin shocks and the dosage of insulin was reduced to 40 units and later to 15 units daily. She was later admitted to hospital unconscious. Large amounts of glucose were given intravenously, but she expired after two days without regaining consciousness. During the last three days numerous examinations of the urine for acetone were made, but on only two occasions was a trace reported. The postmortem examination showed

that a large part of the pituitary gland had been destroyed by hemorrhage.

In correspondence relating to Williams' case, Hurwitz[8] cited a case in which a temporary and reversible damage of the pituitary gland was presumed to occur. A 19 year old primigravid patient, who had diabetes of one and a half year's duration was admitted to hospital with generalized convulsions, elevated blood pressure and albuminuria. After the delivery she had convulsions with hypoglycemia. The insulin dose was reduced and insulin completely omitted for a period of thirteen days, then insulin again was needed and she was discharged with almost the usual dose. This case is not quite clear; the temporary reduced insulin requirement might have been the consequence of an impaired liver function.

The eighth and last case mentioned was published by Israel and Conston[9] and deals with a white female patient, aged 30 years, diabetic since the age of 14. She was pregnant five times over a period of ten years. The fourth labor, in 1947, was complicated by a massive hemorrhage requiring blood transfusion. Several months later, the patient's insulin requirement began to diminish and she experienced repeated insulin shocks. The use of insulin was discontinued in May 1948, and in spite of this the fasting blood sugar was repeatedly found within normal range. During the fifth pregnancy the patient was excessively fatigued. No sugar was found in the urine. Examination of the eyegrounds was not reported. A classical cesarean section was performed in April 1949. A few minutes after the incision the patient became dyspneic and unconscious. Death occurred. The diagnosis of Simmonds' disease was shown by the postmortem examination. Two-thirds of the anterior lobe of the hypophysis was replaced by a mucin-like material and there was a rim of normal hypophyseal tissue surrounding the necrotic area. The adrenals showed cortical atrophy and the thyroid gland showed evidence of diminished activity microscopically. In the pancreas extensive atrophy of the islets of Langerhans was noted.

COMMENT

The clinical course in our case follows the well known pattern of the Houssay phenomenon in clinical and experimental biology. A female with long-standing diabetes acquired pituitary damage in the course of pregnancy and delivery complicated by severe postpartum hemorrhage—a type of pituitary lesion described especially by Sheehan.[10] The symptoms were characteristic of Simmonds' disease: loss of sexual function, loss of axillary and public hair, subnormal basal metabolism, low blood-pressure with orthostatic hypotension, highly increased sensitivity to insulin and an amelioration of the diabetic disorder. The unique finding in this case was the disappearance of diabetic vascular lesions in the eyes. These observations may contribute some hint regarding the pathogenesis of diabetic retinopathy.

It can be concluded that retinopathy with numerous hemorrhages and waxy exudates can disappear and may be curable, and that the lesion is most likely a consequence of metabolic hormonal disorder in diabetes. It seems not only to be caused by the lack of insulin, but, perhaps in a higher degree, the unrestrained action of the pituitary or cortical hormones, or more likely the predominance of unusual pathways in metabolism. This concept is in accordance with the recent paper by Becker[11] in which he claims to have shown that injections of corticotropin into alloxan diabetic rabbits can produce retinal microaneurysms.

Of course, it is impossible through the clinical observation of this single, complicated case to identify the cause of the vascular damage in diabetics, but this may stimulate further research and strengthen efforts at better control of the metabolic disorder in our diabetics. Possibly, consideration might be given to some means of reducing the function of the pituitary gland or adrenal cortex in young patients with severe retinopathy.

SUMMARY

A woman born in 1915, who had diabetes develop in 1924, showed diabetic retinopathy in 1945. After pregnancy in 1945, she developed typical Simmonds' disease (Sheehan type). She showed a highly increased sensitivity to insulin and no longer had a tendency to ketosis. A diet which would normally be ketogenic failed to cause ketonemia or ketonuria until cortisone was administered; the same observation was made in another case of Simmonds' disease without diabetes.

In 1949, the retinopathy was diminished and in 1951 it was no longer present. It can be concluded that diabetic retinopathy is reversible and that retinopathy most likely is a consequence of metabolic disorder.

The development of Simmonds' disease in diabetics is rare. This case is the ninth in medical literature.

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CHRONIC ILLNESS AND SENESCENCE

In the United States in the year 1900 the average life expectancy at birth was 47 years; in 1951 boy babies had an average life expectancy of more than 67 years and girl babies an expectancy of over 71 years. This increment in longevity of over 20 years in half a century, dramatic as it is, is not an unmixed blessing. The toll of prolonged disability of varying degree consequent to chronic illness is so immense as to be truly immeasurable. The burdens of chronic disease, both individually and collectively, are the source of greater tragedy than death from acute illness.

The problems of chronic illness and those engendered by the increasing number of the aging and aged in our population are not identical, but the two areas overlap extensively. Aging per se does not necessarily imply chronic illness, but most of the disablement, misery, and uselessness of those past the so-called prime of life are consequent to chronic progressive disease and not to age alone. Chronic illness is, of course, not limited to those in the senescent period of life. Nevertheless, both the incidence of chronic illness and the degree of disability therefrom are markedly increased after age 40. At age 30 approximately 6 persons per thousand are chronically invalided; at age 40 10 per thousand; and at age 50 15 per thousand; at age 60 28 per thousand; and at age 70 about 50 per thousand.[1] According to the Metropolitan Life Insurance Company's studies,[2] in the year 1901 approximately 53.5 per cent of all deaths were due to chronic disease, whereas in 1945 the chances of untimely dying from chronic disease (instead of from acute disease, external violence, and all other causes) had increased to 82 per cent.

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—From *Chronic Illness and Senescence, by Edward J. Stieglitz, M. D.*, in *The Journal* of the American Medical Association, October 4, 1952

X-RAY THERAPY IN RETINOPATHY

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Over a period of 28 months, we have employed x-ray therapy in a series of cases of diabetic retinopathy of advanced degree, most of whom exhibited a proliferating retinitis and new blood vessel formation. We believe that the results obtained, even after this short interval, have been encouraging enough to warrant publication of a preliminary report and also to stimulate further work along this line.

Our studies were undertaken after Guyton and Reese[1] published in 1948 a preliminary report on the use of roentgen therapy in a series of 14 cases with "ocular diseases characterized by retinal and vitreous hemorrhages with secondary fibrous tissue formation and with new-formed blood vessels extending into the vitreous." Of their total cases treated with irradiation directed to the posterior ocular segment there were 12 cases of Eales's disease, and two cases of diabetes with retinitis proliferans. The roentgen therapy appeared to cause two main effects—a diminution in the newly formed vessels, and, in the cases of Eales's disease, of the fibrous tissue. In the two cases of diabetic retinitis proliferans there was a marked diminution of the new formed vessels but a continuation of the retinal hemorrhages; in one, a fresh vitreous hemorrhage developed five months after treatment.

In view of the effect of the irradiation on the fibrous tissue proliferation and the new vessel formation, we thought that a series of cases with diabetic retinopathy with retinitis proliferans and neovascularization, particularly the so-called "desperate" or "hopeless" cases, should be given a course of roentgen therapy to the posterior ocular segment but in smaller total doses than those used by Guyton and Reese. The dose agreed upon was 2400 r., considerably below the total dose of 3500 to 15,000 r. employed by Guyton and Reese. This figure was chosen since it would allow for further courses of treat-

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ment and still remain below the normal tissue tolerance dose for skin and bone of 6,000 r. Treatment has been given in 34 cases, in 18 of which both eyes were irradiated.

SELECTION OF CASES

The presence of diabetic retinopathy with varying amounts of proliferating retinitis and neovascularization in one or both eyes was the main criterion in the selection of cases. One patient who had only multiple hemorrhages in the retina, without proliferative changes and new vascularization were seen by either the ophthalfour diabetic patients with a total of 52 treated eyes were observed. They ranged from 24 to 74 years of age, with the known duration of diabetes from 3 to 26 years. One patient had been under treatment for only six months, but his history and clinical findings dated its onset at least five years prior to the beginning of treatment. As the patients showing retinitis proliferans and new vascularization were seen by either the ophthalmologist or the physician treating the diabetes, the treatment was suggested to them and the decision was made by the patient. Treatment was carried out by the Radiology Department of the Hospital of the Graduate Schools of Medicine of the University of Pennsylvania. There was no screening of the patients relative to the control of the diabetes, although, after irradiation, an attempt was made to maintain control as completely as possible. No change was made in the routine of the patient. In cases in which rutin, alone or with Vitamin C, was being used, it was continued but not added to the therapy in the other cases. The majority of patients were treated as out-patients.

The ophthalmologic examination was made at the end of the series of treatments. An attempt was made to check the condition of patients by both the internist and the ophthalmologist at monthly intervals for six months, then as desired. The patients were instructed to report any changes in the eye to the ophthalmologist so that an examination could be made as soon as possible.

Any undue effects from the irradiation were referred to the radiologist for examination and treatment. Erythema and swelling of the skin in the temporal region was the most marked reaction, occuring in about 15 per cent of the cases and clearing in about a week, either with or without treatment. Treatment consisted in the local application of Aquaphor ointment. No ulceration or other complications developed. Slight temporary pigmentation occurred in some patients.

TECHNIC OF ROENTGEN THERAPY

The technic used was a modification of that used by Martin and Reese[2] "to give large doses of roentgen radiation to the posterior ocular segment with minimal effects on the vulnerable anterior segment." A lateral posterior orbital portal, measuring 2 x 2 cm., placed so that the posterior edge overlies the lateral orbital rim approximately 1.5 cm. and the anterior edge overlies the globe about 0.5 cm., was used. The following factors were utilized: 140 kilovolts, filter, 4 mm. aluminum; half-value layer, 4 mm. of aluminum; skin-target distance 21.5 cm; 5 milliamperes. The dosage consisted of a daily dose of 300 r. (air) for eight consecutive days for a total of 2400 r. (air) delivered only through a lateral posterior orbital portal. Forty-six eyes (88 per cent) were treated with the minimum dose of 2400 r. (air), three eyes (6 per cent) with 3600 r. (air), two eyes (4 per cent) with 3900 r. (air), and one eye (2 per cent) with the maximum of 4800 r. (air). Additional courses of therapy depended on the judgment of the ophthalmologist.

TABLE 1 Results of Treatment

Improved	17	(33 per cent)
Slightly Improved	12	(23 per cent)
Unchanged	16	(31 per cent)
Worse	7	(13 per cent)

In 17 cases (33 per cent) there was improvement. While definite, it varied considerably in degree. The gain in visual acuity varied from moderate to very marked, and the recession in the retinitis proliferans and the neovascularization varied in the same manner. Three cases illustrate these results.

CASE 17—a man aged 45 years whose vision had been limited to "counting fingers" only for at least a year prior to roentgen therapy, showed improvement in vision to 6/22 in one eye after treatment; this enabled him to resume his work. Unfortunately he died in diabetic coma six months after the treatment was completed.

CASE 5—a 56 year old woman had marked vascular changes and her vision had been limited to light perception only prior to treatment. Her vision improved to 6/30 in the right eye and 6/100 in the left eye, and the improved vision was maintained for at least one year. She died of a cerebrovascular accident twenty-eight months following therapy.

CASE 27—a 62 year old man had his right eye removed because of a hemorrhagic glaucoma; the vision in the

left eye was limited to only ½/150. After treatment the vision in this eye improved to 6/45. This enabled him to get around unassisted. The improvement has been maintained for one year since therapy.

In all three cases there was marked recession in both fibrous tissue and newly formed vessels.

In 12 cases (23 per cent) there was slight improvement in either visual acuity or in the state of the retinitis proliferans or the neovascularization.

In 16 cases (31 per cent) there was no change in the visual acuity or in the state of the fibrous tissue proliferation or the neovascularization.

In 7 cases (13 per cent), there was further deterioration in the vision and an increase in both the retinitis proliferans and the newly formed vessels. The seven eyes in this group were in five most complicated cases. Two patients were juvenile diabetics, below the age of thirty, who had all the manifestations of Kimmelstiel-Wilson's syndrome. Two patients were elderly diabetics who had advanced vascular disease; one had had recent operations for advanced glaucoma with marked visual field defects. The fifth patient was a 47 year old female physician who had poorly controlled diabetes and active tuberculosis.

The ophthalmoscopic findings paralleled, to a great extent, those seen by Guyton and Reese in their cases of Eales's disease. The greatest effect of the roentgen therapy, as in their cases, was in the appearance of the newly formed blood vessels, even with the moderate doses that were used in this series. No effect on the vessels whatsoever was noted during or immediately after the period of irradiation. Within three to five weeks later, diminution in caliber was noted; some of the smaller vessels disappearing. The maximum effect was attained in approximately eight weeks. By this time the medium-sized vessels showed marked diminution in caliber but the larger vessels were not appreciably affected. This regression of the new vessels occurred in the first three groups but to a much less extent in the fourth group. In this group, while regression of the smaller vessels, and even some of the medium-sized vessels occurred, the change appeared only temporarily. New vessels continued to appear later, but no more rapidly than before. The part played by the newly formed vessels would naturally be less than that played by the opaque fibrous tissue. In one case where a thrombosis of the central retinal vein occurred in association with advanced vascular pathology and associated with Kimmelstiel-Wilson's syndrome, it was thought that the roentgen therapy was not a factor in the development of the thrombosis.

Regression in the retinitis proliferans to some extent paralleled the regression of the newly formed blood vessels, although any regression in the denser fibrous tissue would be naturally less than the more vulnerable blood vessels. Those cases which became worse not only showed subsequent increase in the newly formed vessels, as noted above, but further progressive increase in the fibrous tissue mass. The position of the retinitis proliferans in the vitreous determined the visual impairment. A small fibrous strand in the macular region would have a more profound effect on vision than a large mass in the periphery. A mass of fibrous tissue overhanging the macular area would profoundly interfere with vision, but if the mass were reduced in size the macula would be uncovered and vision improved.

There was no appreciable change in the retinal hemorrhages or exudates after roentgen therapy. The number and position of the hemorrhages fluctuated over a wide range in some cases, and in the whole series there seemed to be no correlation between their appearance and disappearance and the roentgen therapy itself. Their changes appeared, in this series, to be more influenced by the control of their diabetes than by any extraneous factor. This was particularly true in the cases in which multiple retinal hemorrhages, without proliferation or neovascularization, were the only ophthalmoscopic changes. No integral change in the retinal vessels themselves could be attributable to the roentgen therapy over the period of time the cases were observed.

During the time the observations were carried out, no effect of the roentgen therapy on the crystalline lens could be found. Prior to the therapy, a number of the cases showed a varied degree of lens changes. At their latest examination, a few of the cases showed further progression in the lens changes, but not out of proportion to those changes expected without irradiation. The importance of most careful and meticulous use of the irradiation, with the roentgen rays directed toward the posterior pole of the globe, cannot be overstressed in view of the possibility of producing radiation cataract.

COMMENT

Prior to the use of insulin, diabetic retinopathy with proliferating retinitis and newly formed blood vessels (neovascularization) was not the problem that it is today. Diabetic retinopathy with hemorrhages and exudates was found mostly in the older patient with mild diabetes that could be controlled by diet. With the

FIGURE 2.

			DIABETES					EYE FINDINGS BEFORE TREATMENT						
Case	Sex	Age	Duration	Control	Daily dose of insulin	Daily dose of rutin	Ocular complaints	Duration	Eye	Vision	Vitreous Hemorrhages	Retinal Hemorrhages	Neovascularization	Proliferating Retinitis
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	M	30	24	Good	15 PZ	120 R+C	Loss vision	2 mo.	R	HM	++++	—	—	—
									L	6/9	0	++	+++	+++
2	F	53	12	Poor	25 PZ	80 R+C	Blurred vision	2 mo.	R	6/9	0	+++	0	0
							Blurred vision	2 mo.	L	6/30	0	+++	0	0
3	M	35	10	Fair	44 R 22 PZ	—	Loss vision	1 wk.	R	2/60	++	++	+++	+++
									L	6/9	0	++	+++	+++
4	M	24	21	Fair	60 NPH	240 R+C	Loss vision	4 mo.	R	LP	++	++++	++++	++++
									L	6/15	0	++++	++++	++++
5	F	56	23	Good	15 NPH	180 R+C	Loss vision	2 yrs.	R	LP	0	+++	++++	++++
							Loss vision	2 yrs.	L	LP	0	+++	++++	++++
6	F	48	14	Good	45 NPH	240 R+C	Failing vision	1 yr.	R	6/100	0	++++	++	++
							Failing vision	1 yr.	L	6/100	0	++++	++	++
7	F	26	10	Fair	25 NPH	120 R+C	Poor vision	5 yrs.	R	6/45	0	++++	++++	+++
							Poor vision	5 yrs.	L	6/45	0	++++	++++	+++
8	F	60	17	Good	0	120 R+C	Loss vision	3 yrs.	R	1/60	0	+	++++	++++
							Sudden loss	4 yrs.	L	LP	1948	+	++++	++++
9	F	37	18	Fair	55 NPH	360 R+C	Failing vision	6 mo.	R	6/9	0	+++	++++	++++
							Sudden loss	14 mo.	L	HM	1950	+++	++++	++++
10	F	69	16	Excellent	0	120 R+C	Gradual loss	8 yrs.	R	CF	0	+++	++++	++++
							Gradual loss	8 yrs.	L	6/150	0	+++	++++	++++
11	F	44	10	Poor	15 Glob.	240 R+C	Sudden loss	2 yrs.	R	LP	1950	—	—	—
							Gradual loss	2 yrs.	L	1/150	0	++	++++	++++
12	M	29	21	Poor	30 Glob.	240 R+C	Gradual loss	9 mo.	R	6/22	0	+++	0	0
							Gradual loss	9 mo.	L	3/60	?	+++	+	+
13	M	55	3	Poor	20 PZ	—	Gradual loss	3 yrs.	R	3/60	0	++	+++	++++
							Gradual loss	3 yrs.	L	6/150	0	+++	++++	++++
14	M	51	6	Fair	20 PZ	—	Gradual loss	4 yrs.	R	6/15	0	+++	0	0
							Gradual loss	4 yrs.	L	3/45	0	+++	++	++
15	M	69	10	Poor	20 PZ	120 R+C	Retinopathy found after cataract surg.		R	6/9	0	++	0	0
									L	6/45	0	++	+	+
16	F	51	14	Fair	20 R 20 PZ	180 R+C	Gradual loss	6 mo.	R	3/60	0	+++	+++	+++
							Gradual loss	6 mo.	L	6/150	0	+++	++	++
17	M	45	17	Poor	30 NPH	180 R+C	Gradual loss	2 yrs.	R	CF	0	++	++++	++++
							Gradual loss	2 yrs.	L	CF	0	++	++++	++++

EXPLANATION OF CHART

Column 4. Length of time case has been under treatment.

Column 5. Control—Classified Excellent, Good, Fair or Poor (Wilson, Root, Marble[9]).

Column 12. Vitreous hemorrhage—based on history and ophthalmoscopic examination.

Column 13. Retinal hemorrhages—ranging from (+) occasional to (++++) profuse.

Column 14. Neovascularization or new formed vessels in vitreous—Graded from (+) a single tuft or fine arborizing vessels to (++++) groups of large caliber vessels with a dense network of arborizing vessels approaching the classical descriptive term of "rete mirabile".

Column 15. Retinitis proliferans or fibrous tissue extending into the vitreous—Graded from (+) a single band or several small, fine, veil-like strands to (++++) a number of large, heavy bands or masses of fibrous tissue extending into the vitreous.

	X-RAY TREATMENT			EYE FINDINGS AFTER TREATMENT							
Comments	Date	Roentgen Dosage	Follow Up Period	Eye	Vision	Vitreous Hemorrhages	Retinal Hemorrhages	Neovascularization	Proliferating Retinitis	Subjective Changes	Results
16	17	18	19	20	21	22	23	24	25	26	27
Unable to see fundus	5/51	2400	12 mo.	R	CF	Organized	—	—	—	Same	Same
Much venous change	2/51	2400	15 mo.	L	6/12	0	Same	Less	Less	Better	Slightly improved
	4/52	2400	1 mo.	R	6/9	0	Same	0	0	Diabetes better	Same
	8/51	2400	9 mo.	L	6/9	0	Same	0	0	controlled	Same
Much vascular change	9/51	2400	9 mo.	R	6/9	0	Same	Less	Less	Better	Improved
				L	6/9	0	Same	Same	Same	Same	
Kimmelsteil-Wilson	2/52	2400	3 mo.	R	CF	0	Less	Slightly less	Slightly less	Same	Slightly improved
syndrome	2/52	2400	3 mo.	L	6/7.5	0	Less	Less	Less	Better	Improved
Hypertensive vascular	11/49	2400	26 mo.	R	6/30	0	Same	Less	Less	Better	Improved
changes. Amputation	11/49	2400	26 mo.	L	6/100	0	Same	Less	Less	Better	Improved
Early nuclear cataracts, both eyes	9/51 1/52	3600	8 mo.	R	6/45	0	Less	Less	Less	Better	Improved
	8/51 2/52	3900	8 mo.	L	6/30	0	Less	Less	Less	Better	Improved
Able to read headlines	10/51	2400	7 mo.	R	6/12	0	Same	Less	Less	Much improved	Improved
only for past 4-5 yrs.	11/51	2400	6 mo.	L	6/12	0	Same	Less	Less	Able to read	Improved
Hypertensive cardio-	10/50	2400	18 mo.	R	1/60	0	Same	Less	Less	Better	Slightly improved
vascular disease	10/50	2400	18 mo.	L	1/60	0	Same	Less	Less	Better	Slightly improved
Hypertension	6/51	2400	11 mo.	R	6/9	0	Same	Same	Same	Same	Same
Rete mirabile	6/51	2400	11 mo.	L	CF	0	Same	Same	Same	Same	Same
Profound vascular disturbances	2/51	2400	15 mo.	R	6/60	0	Same	Less	Less	Much better	Improved
				L	6/150	0	Same	Same	Same	Same	
Absolute Glaucoma				R	LP	—	—	—	—	—	
Rete mirabile	11/51	2400	6 mo.	L	2/60	0	Same	Less	Less	Less	Slightly improved
Much vascular change	8/51	3600	9 mo.	R	2/100	0	Same	More	More	Worse	Worse
Kimmelsteil-Wilson	12/51										
syndrome	7/51 1/52	3600	10 mo.	L	6/100	0	Same	More	More	Worse	Worse
Old retinal detachment	1/51	2400	16 mo.	R	2/150	0	Same	Less	Less	Slightly better	Slightly improved
				L	6/150	0	Same	Same	Same	Same	
Hypertensive cardio-				R	6/15	0	Same	Same	Same	Same	
vascular disease	3/52	2400	2 mo.	L	3/45	0	Same	Same	Same	Same	Same
Cataract operation				R	6/9	0	+	0	0	Same	
Oct. 1951, both eyes	2/52	2400	3 mo.	L	6/45	0	+	0	0	Same	Same
Kimmelsteil-Wilson	11/51	2400	6 mo.	R	6/150	0	Same	Less	Less	Slightly better	Slightly improved
syndrome	12/51	2400	6 mo.	L	6/100	0	Same	Less	Less	Slightly better	Slightly improved
Retinal detachment	8/50	2400	5 mo.	R	CF	0	Same	Same	Same	Died in coma	Same
	8/50	2400	5 mo.	L	6/22	0	Same	Less	Less	Feb. '51	Improved

Column 18. Roentgen dosage—total dosage in r's (air).

Column 22. Vitreous hemorrhages following start of therapy.

Column 23. Retinal hemorrhages—noted as less, same, or more than the number noted in pre-treatment examination.

Column 24. Neovascularization—noted as less, same, or more than in pre-treatment examination.

Column 25. Retinitis proliferans—noted as less, same, or more than in pre-treatment examination.

Column 26. Results—depended on patient's observations and ophthalmoscopic examination.

IMPROVED—definite improvement in patient's visual acuity and a definite marked diminution in the proliferating retinitis and neovascularization.

SLIGHTLY IMPROVED—either some improvement in vision without noticeable recession in the proliferation and/or the neovascularization.

SAME or UNCHANGED—no change in either the visual acuity or the proliferation and neovascularization.

WORSE—further deterioration in visual acuity with an increase in fibrosis and neovascularization.

			DIABETES					EYE FINDINGS BEFORE TREATMENT						
Case	Sex	Age	Duration	Control	Daily dose of insulin	Daily dose of rutin	Ocular complaints	Duration	Eye	Vision	Vitreous Hemorrhages	Retinal Hemorrhages	Neovascularization	Proliferating Retinitis
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
18	M	47	½	Fair	Diet	80 R	Loss vision	18 mo.	R	6/22	1950	++	++++	++++
							Loss vision	10 mo.	L	6/150	1951	++	++++	++++
19	M	30	20	Poor	80 NPH	360 R+C	Blurred vision	6 mo.	R	6/9	0	++++	+	+
							Loss vision	1 yr.	L	3/60	?	++	++++	++++
20	F	70	18	Poor	10 NPH	80 R	Blurred vision	1 yr.	R	6/9	0	++++	0	0
							Blurred vision	1 yr.	L	6/15	0	++++	++	+
21	M	30	17	Fair	50 R	120 R+C	Loss vision	1 yr.	R	6/22	0	++	++	++
					25 PZ		Sudden loss	1 mo.	L	HM	++	+++	++++	++++
22	M	47	2	Fair	25 NPH	60 R	Failing vision	1 yr.	R	3/45	0	++	++	++
							Failing vision	1 yr.	L	1/60	0	++	+++	+++
23	M	57	15	Good	12 PZ	240 R+C			R	6/5	0	+++	0	0
							Cloudy vision	1 mo.	L	6/22	0	+++	+	+
24	M	74	16	Poor	60 NPH		Failing vision	2 yrs.	R	6/30	0	+++	++	++
							Failing vision	2 yrs.	L	6/22	0	+++	++	++
25	F	66	25	Poor	15 R	120 R+C	Failing vision	2 yrs.	R	6/100	0	--	—	—
					10 PZ		Failing vision	2 yrs.	L	6/22	0	++	++	++
26	F	47	26	Fair	20 NPH	360 R+C	Blurred vision	1 yr.	R	6/6	0	+++	0	0
							Blurred vision	1 yr.	L	6/6	0	+++	+	+
27	M	62	20	Good	10 PZ	80 R+C			R	—— Enucleated Hemorrhagic Glaucoma, 1950				
							Sudden loss	2 mo.	L	½/150	2 mo.	++	+++	+++
28	M	54	7	Poor	20 PZ	—	Failing vision	2-3 yrs.	R	6/60	0	+++	+	+
							Failing vision	2-3 yrs.	L	6/60	0	+++	+	+
29	F	59	15	Poor	25 Glob.	240 R+C	Poor vision	6 mo.	R	1/60	0	+++	+	+
							Poor vision	6 mo.	L	1/60	0	+++	+	+
30	M	47	2	Good	30 NPH	360 R	Sudden loss	1 mo.	R	FM	1 mo.	--	--	--
									L	6/6	0	++	0	0
31	F	73	7	Fair	15 PZ	—	Poor vision	5 yrs.	R	2/60	0	++	+++	+++
							Failing vision	1 yr.	L	6/9	0	++	+	+
32	F	25	15	Poor	50 NPH	180 R+C	Failing vision	1 yr.	R	6/22	0	+++	++++	++++
							Failing vision	1 yr.	L	6/22	0	+++	++++	++++
33	M	52	8	Poor	20 PZ	180 R+C	Poor vision	6 mo.	R	LP	0	+++	++++	++++
									L	6/6	0	+	0	0
34	F	68	4	Poor	0	180 R+C	Failing vision	2 yrs.	R	HM	0	++++	+++	+++
							Failing vision	2 yrs.	L	6/30	0	++++	+++	+++

EXPLANATION OF CHART

Column 4. Length of time case has been under treatment.

Column 5. Control—Classified Excellent, Good, Fair or Poor (Wilson, Root, Marble[9]).

Column 12. Vitreous hemorrhage—based on history and ophthalmoscopic examination.

Column 13. Retinal hemorrhages—ranging from (+) occasional to (++++) profuse.

Column 14. Neovascularization or new formed vessels in vitreous—Graded from (+) a single tuft or fine arborizing vessels to (++++) groups of large caliber vessels with a dense network of arborizing vessels approaching the classical descriptive term of "rete mirabile".

Column 15. Retinitis proliferans or fibrous tissue extending into the vitreous—Graded from (+) a single band or several small, fine, veil-like strands to (++++) a number of large, heavy bands or masses of fibrous tissue extending into the vitreous.

	X-RAY TREATMENT			EYE FINDINGS AFTER TREATMENT							
Comments	Date	Roentgen Dosage	Follow Up Period	Eye	Vision	Vitreous Hemorrhages	Retinal Hemorrhages	Neovascularization	Proliferating Retinitis	Subjective Changes	Results
16	17	18	19	20	21	22	23	24	25	26	27
	12/51	2400	6 mo.	R	6/9	0	Same	Slightly less	Slightly less	Same	Slightly Improved
	12/51	2400	6 mo.	L	6/30	0	Same	Less	Less	Better	Improved
Much vascular change	6/51	2400	11 mo.	R	6/30	0	Worse	Worse	Worse	Worse	Worse
Kimmelsteil-Wilson syndrome	6,9,11/51	4800	11 mo.	L	HM	0	Worse	Worse	Worse	Worse	Worse
Hypertensive cardiovascular disease	3/52	2400	2 mo.	R	6/9	0	Same	Same	Same	Same	
				L	6/15	0	Same	Same	Same	Same	Same
Rete mirabile	1/50	2400	28 mo.	R	6/9	0	Same	Less	Less	Better	Improved
	12/49	2400	27 mo.	L	6/22	0	Less	Less	Less	Better	Improved
Much venous change	2/52	2400	3 mo.	R	6/30	0	Same	Less	Less	Better	Improved
	2/52	2400	3 mo.	L	6/60	0	Same	Less	Less	Better	Improved
				R	6/5	0	Same	Same	Same	Same	
	2/52	2400	3 mo.	L	6/12	0	Same	None	Less	Better	Slightly Improved
					Cataract						
Hypertensive Cataracts, both eyes	3/51	2400	16 mo.	R	2/150	0	Same	Worse	Worse	Worse	Worse
	5/51	2400	12 mo.	L	6/30	0	Same	Same	Same	Same	Same
Mature cataract. Much vascular change. Glaucoma operation both eyes, 1951	2/51	2400	3 mo.	R	6/150	0	Same	Same	Same	Same	
				L	6/100	0	Same	Worse	Worse	Worse	Worse
						March					
Active Tuberculosis				R	6/150	1952	Same	Worse	Worse	Much Worse	
	12/51	2400	5 mo.	L	6/15	0	Same	Worse	Worse	Worse	Worse
				R	Enucleated Hemorrhagic Glaucoma. 1950						
"Hopeless"	5/51	2400	12 mo.	L	6/45	0	Same	Less	Less	Better	Improved
Hypertensive cardiovascular disease	2/52	2400	3 mo.	R	6/60	0	Same	Same	Same	Same	Same
	2/52	2400	3 mo.	L	6/60	0	Same	Same	Same	Same	Same
Hypertensive cardiovascular disease	1/52	2400	4 mo.	R	1/60	0	Same	Same	Same	Same	Same
	2/52	2400	3 mo.	L	2/60	0	Same	Same	Same	Same	Same
Repeated vitreous hemorrhages clearing in 2 months	10/51	3900	7 mo.	R		3 in					
	2/52					13 mo.	Same	0	0	Better	Same
				L	6/6	0	Same	0	0	Same	
Much vascular change	12/50	2400	6 mo.	R	1/60	0	Same	Less	Less	Same	Slightly Improved
				L	6/9	0	Same	Same	Same	Same	
Kimmelsteil-Wilson syndrome				R	6/60	1 mo.	Same	Same	Same	Same	
Much vascular change	1/52	2400	4 mo.	L	6/12	0	Less	Less	Less	Better	Improved
Retinal detachment	1/50	2400	28 mo.	R	NLP	0	Same	Same	Same	Same	Same
				L	6/6	0	Same	0	0	Same	
Hypertensive cardiovascular disease	3/52	2400	2 mo.	R	2/60	0	Same	Slightly less	Slightly less	Slightly better	Slightly Improved
				L	6/30	0	Same	Same	Same	Same	

Column 18. Roentgen dosage—total dosage in r's (air).

Column 22. Vitreous hemorrhages following start of therapy.

Column 23. Retinal hemorrhages—noted as less, same, or more than the number noted in pre-treatment examination.

Column 24. Neovascularization—noted as less, same, or more than in pre-treatment examination.

Column 25. Retinitis proliferans—noted as less, same, or more than in pre-treatment examination.

Column 26. Results—depended on patient's observations and ophthalmoscopic examination.

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discovery of insulin and the increase in longevity of patients, resulting from its widespread use, the incidence of diabetic retinopathy has steadily increased. This is illustrated by Wagener's figures[3]. He found that 8.3 per cent of the diabetics examined in 1921 showed retinopathy; 17.7 per cent in 1934 and 30.6 per cent in 1945. Ballantyne[4] found retinopathy in 31.7 per cent of 561 patients of all ages in 1946. Friedenwald's office records[5] show that it was three times as frequent in 1950 as in 1924. The marked increase in retinopathy in juvenile diabetics is more striking. Again quoting Wagener[3]—in 1921, none of the patients with retinopathy was below the age of 40; in 1934, 4.3 per cent were below the age of 40; and the figure was tripled to 12.8 per cent (or 8.3 per cent of the total) in 1945. In 6 per cent of cases of retinopathy in Ballantyne's series,[4] the patients were in the 10 to 19 year age group; 30 per cent in the 40 to 49 age group; and 46 per cent in the 70 years and over group. In the series presented here, 9 of the 34 patients, (or 26 per cent) with advanced retinopathy were below the age of 40 years, while 7 (or 21 per cent) were 30 years of age or younger.

The early manifestations of diabetic retinopathy are not the direct concern of this discussion, but are of interest indirectly as the precursors or predecessors of the proliferating retinitis and neovascularization.

Duke-Elder[26] divides the conditions given the descriptive term, retinitis proliferans, into two types: a) The classical type in which fibrous tissue follows retinal hemorrhages breaking through into the vitreous cavity, characterized by the formation of dense opaque white membranes of fibrous tissue, (derived from the mesoblastic elements associated with the retinal vessels), with little vascularization. This type is purely degenerative and serves no useful function. b) The second type, which depends on circulatory impairment and degenerative vascular disease, occurs always at the disc. This type serves a useful function in that it attempts to supply collateral circulation and is therefore characterized by profuse formation of newly formed blood vessels (neovascularization). In actuality, the latter represents the condition of new vessel formation, varying from a single vessel with a few fine delicate branches to the large anastamotic networks, spoken of as rete mirabile. Klien[27] later confirmed this classification.

The difference between the two types appears to be in the relation of fibrous tissue to new vessels and, in some cases, to the site of origin. In the former, there is a marked excess of fibrous tissue and a paucity of new vessels, while in the latter there is an excessive amount of neovascularization and a small amount of fibrous tissue. The classical type may originate from any bleeding point along any of the retinal vessels, although in many cases it occurs close to the disc where the retinal mesoblastic tissue is massed. The second type originates only near the disc. In the later stage of diabetic retinopathy, as in most of the cases of the present series, it is impossible to tell from which type the proliferation originated, since both of the etiological factors have been present at one stage or another, namely; the occurrence of bleeding points into the retina and vitreous and degenerative vascular disease with circulatory impairment.

Loss of vision in the later stages of diabetic retinopathy can come from a number of causes: a hemorrhage into the macular region; a gross hemorrhage into the vitreous; obstruction of the macular region by a mass of fibrous tissue; or one of the later complications of glaucoma or retinal detachment, the latter resulting from the contraction of the fibrous tissue bands pulling on the retina. With the absorption of the retinal or vitreous hemorrhage, the vision may improve; but usually with obstruction of the macula by the proliferative masses (or following the intervention of glaucoma or retinal detachment,) improvement is rarely found.

The course of events in many cases exhibiting proliferating retinitis and neovascularization is a slow, steady progression in both processes. Guyton and Reese[1] felt that the presence of blood in the vitreous, even when not visible by ophthalmoscopic examination, stimulated the formation of fibrous tissue and new vessels and that the production of these newly formed vessels created new sources of bleeding and in this way set up a "vicious cycle." It was upon this thought that the reason for their use of roentgen ray therapy was based, and their attempt to destroy the newly formed blood vessels and thus break up this "vicious cycle" of bleeding and proliferation.

In view of the Guyton and Reese findings of diminution in the newly formed vessels, and to a lesser extent regression of fibrosis after irradiation, we undertook further studies to evaluate the effect of roentgen therapy, modified by using moderate doses, in advanced cases of diabetic retinopathy. The aims were a) to reduce the mass of the fibrous tissue and the newly-formed blood vessels, particularly when present in the region of the posterior pole of the globe. In this way, the obstructing opaque masses from the visual line would be removed, thus improving the visual acuity; b) to alter the "vicious cycle"; to prevent

further bleeding by obliterating the smaller newly-formed vessels. In this way, the progressive nature of the proliferating retinitis and the increase in the neovascularization would be retarded.

Since the cause of the basic vascular pathology in the retinopathy is still unknown, no effect by the roentgen therapy was anticipated or found in the retinal hemorrhages, exudates, or microaneurysms described by Friedenwald,[5] Ballantyne,[28] Ballantyne and Lowenstein,[29] and Ashton.[30]

It is to be emphasized that therapy will be efficacious only when the cause of the retinopathy is found; but in the meantime, some method should be sought to minimize the fibrous tissue proliferation and neovascularization increase which is so disastrous to vision. It is felt that the results reported here are optimistic enough to warrant a preliminary report and to stimulate further studies along this line.

SUMMARY

During 28 months moderately intensive roentgen therapy was given in a series of cases of advanced diabetic retinopathy characterized by retinitis proliferans and newly-formed blood vessels extending into the vitreous. The series included 34 diabetic patients, 18 of whom had both eyes treated.

The irradiation technic was a modification of that devised by Martin and Reese to avoid damage to the anterior ocular segment in the treatment of retinoblastoma. A total dose of 2400 r. was used in 88 per cent of the cases. In the remainder greater doses were used, the greatest being 4800 r.

In 33 percent of the eyes treated, there was some degree of regression of the newly formed blood vessels and, to a lesser extent, of the retinitis proliferans, with some improvement of the visual acuity. In 23 per cent there was either some regression of the fibrosis and the neovascularization or some improvement of the visual acuity. In 30 per cent, there was no change, and in 13 per cent there was progression of the proliferation and neovascularization and further deterioration of vision.

It is emphasized that the therapy described was directed toward the advanced diabetic retinopathy with retinitis proliferans and newly formed blood vessels. It was not concerned with early diabetic retinopathy, the cause of which is still unknown at this time.

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THE COMPLEXITIES OF CHRONIC ILLNESS AND SENESCENCE

The immensity, complexity, and urgency of the problems of chronic illness in senescence need no reiterative emphasis.[3] Age per se is rarely a major factor in this disablement of the elderly; the accumulative injuries of progressive chronic circulatory and metabolic disorders account for the vast majority of incompetent aging and aged. These degenerative diseases have several generic characteristics that conspicuously modify the problems: (1) multiple, variable, largely endogenous etiology, (2) silent asymptomatic onset, (3) persistent progression, and (4) variability and superimposition of several disorders so that sharply defined entities are exceptional. These disorders can not be prevented by the usual wholesale methods of public health and control of the environment. Individualization in medical care is essential. Equally essential are the initiative and self-discipline of the individual patient.

Health in later maturity can not be given; it must be earned. In chronic illness it is most important not to promise either too little or too much. Morale and the necessary efforts toward rehabilitation are vital factors. Violent reactionary depression follows failure of overly optimistic promises. Not infrequently the maintenance of a status quo in health for a person with progressive illness is a major therapeutic accomplishment. The physician fights delaying actions. We must expect to lose every patient ultimately. Nevertheless, the field is full of challenge and reward. In diseases of senescence the physician deals with subtle, insidious changes, which demand the highest diagnostic acumen for their detection, identification, and evaluation, and the greatest therapeutic skill individually applied. Geriatric medicine is no area for those who are intellectually lazy.

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From *Chronic Illness and Senescence* By Edward J. Stieglitz, M.D., in the *Journal* of the American Medical Association, October 4, 1952.

The Insulin Content of Blood Plasma

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Gellhorn and Feldmann[1] in 1941, using adrenomedullated hypophysectomized rats, found that the plasma of fed dogs caused a profounder degree of hypoglycemic than that of fasted dogs, the apparent insulin concentration being approximately doubled. Although Gellhorn and Feldman's estimates of insulin concentration are in the same range as we have found, the technic is liable to the criticism that as the test animals' beta cells were not destroyed, the rats' own insulin may have interfered with the assay.

In 1947 Anderson, Lindner, and Sutton[2] published the details of a technique using ADH (adrenomedullated, alloxan diabetic, hypophysectomized) rats. Using these preparations Anderson was able to demonstrate that a perfused pancreas secreted insulin in response to a rise in the glucose concentration of the perfusate, and that the addition of growth hormone interfered in some way with the assayable insulin. An action of growth hormone in the pancreas has also been demonstrated by Bornstein, Reid and Young.[3] The sensitivity of this technic was approximately 1/8000 units of insulin or 0.125 milliunit. In 1948, one of us (J. B.) repeated the work of Anderson with a view to attempting to assay insulin in human plasma. A similar degree of sensitivity was obtained and it was found that if glucose were administered to a dog, blood obtained from the pancreatic vein had an increased insulin concentration. When work commenced with human plasma, we found that the administration of 0.5 to 1.0 ml. plasma was required to produce a hypoglycemic response. The administration of this volume of plasma intravenously to nembutalized ADH rats frequently caused death due to acute cardiorespiratory failure. Accordingly we re-examined the technic with a view to carrying out the assay over a longer period of time and giving the substances under test subcutaneously. It was found by varying the environmental conditions that it was possible to induce a state where the blood glucose concentration varied very little over a period of one hour, and accordingly an assay was constructed using this period of time. The range of sensitivity was from 1/20,000 to 1/2,000 of a unit of insulin (0.05 to 0.5 milliunit).

Here I should like to point out that in my opinion the only reason for the apparent increase in sensitivity is that the assay is carried out on a relatively stable base, whereas Dr. Anderson's assay is obtained on a rising base line. The curves obtained with both technics are very similar. The real advantage of this modification is that larger amounts of plasma can be administered and anesthesia and surgery during the assay are avoided.

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Presented at the meeting of the American Diabetes Association, Chicago, June 8, 1952.

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This technic was then applied to the study of plasma insulin concentration in normal man under the conditions of a glucose tolerance test. It was found that the detectable plasma insulin increased with the rise in blood sugar, reaching a peak when the glucose had been restored to normal and thereafter declining. The details of controls required for such an assay have been published elsewhere.[4] The technic was next applied to the study of diabetic patients. As it had previously been found that in the normal individual, insulin was at an apparent peak two hours after glucose, this period was arbitrarily chosen for the studies in cases of diabetes.

Altogether a control group of 14 normal persons of all ages and 28 "new" cases of diabetes were studied. It was found that the concentration of available plasma insulin of the normal controls varied from 0.24 to 0.40 milliunit per ml. with a mean of 0.34 mu/ml. whereas the cases of diabetes fell into two groups, one group of 15 cases in which no insulin could be detected showed considerable loss of weight and some degree of ketosis as principal clinical characteristics. The other group of 13 cases, in which a range of 0.10 to 0.32 milliunit per ml. was found (with a mean of 0.23 milliunit per ml.), was characterized by the presence of obesity, lack of ketosis and symptoms of various complications of diabetes mellitus rather than those of the syndrome itself. It is interesting to note that the group in which no insulin could be detected included patients of all ages from 5 to 64 which with a mean age of 36, the patients in the second group being preponderantly female, largely over middle age, (an average age of 49.) This leads us to believe that the mild form of diabetes is largely confined to women in the later years of life. These older obese patients in nearly all cases could be stabilized without administration of insulin.

A number of other cases have been studied. Four of the patients showing no insulin in their plasma were studied after they had been stabilized on diet and insulin. The blood was taken at a time when the blood sugar was found to be within the normal range. The plasma insulin under these conditions was found to be about 0.25 milliunit per ml.

Tests were made in two cases showing marked insulin resistance. It was necessary to give over 2000 units per day to depress the blood sugar significantly. In each case blood was taken 1 hour after the injection of 300 units of insulin. No insulin could be detected.

One case of hyperinsulinism with islet carcinoma was studied but an attempt to estimate the insulin concentration in the blood was unsuccessful, as 0.5 ml. of the plasma produced rapidly fatal hypoglycemia in the test animals. In three cases of spontaneous hypoglycemia after gastrectomy, the patients had as one of the major characteristics, normal sensitivity to insulin but a failure of the blood sugar to recover in a normal time, when an insulin tolerance test was performed. Here, glucose was administered and blood samples were taken at 1 and 2 hours; the hypoglycemic attack usually developed at these times. The peak range of insulin concentration was from 0.64 to 0.86 milliunit per ml.

At this stage it must be pointed out that such an assay does not absolutely measure the amount of insulin present but merely detects the excess of insulin over its antagonists absorbed in unit time. Accordingly the finding of a zero value for insulin does not necessarily mean that the patient is failing to secrete the hormone but may merely mean that inhibitors are present in sufficient excess in the plasma to mask completely any insulin effect.

Evidence for these views came to light when we found that following an injection of the plasma of some diabetic patients with no apparent insulin in the plasma there was a marked decrease in the insulin sensitivity of the ADHA (alloxan-diabetic, hypohysectomized adrenalectomized) rats used in the assays. Further evidence demonstrating the presence of a circulating inhibitor in plasma has recently been obtained by Bornstein and Park in the Department of Biological Chemistry, Washington University, St. Louis. Using a specially modified technic of handling the rat diaphragm it has been found that in the presence of the serum of the diabetic rat, the rate of utilization of glucose is depressed as compared with the serum from the fasting normal rat and that this inhibitory action of the serum is abolished by either hypophysectomy or adrenalectomy of the donor animal. Replacement therapy with growth hormone alone or cortisone alone fails to restore the inhibition but the administration of both restores the inhibition; in all cases the inhibition, when present, is reversible by insulin provided a sufficient concentration of insulin is used. It is of interest that the inhibiting substance once present is extremely persistent. In groups of diabetic hypophysectomized rats injected with growth hormone and cortisone the inhibitor was fully present seven days after the last injection of the hormones. This finding we feel is analogous to the finding in the ADHA rats in which the inhibition persisted for varying periods after the injection of plasma but could always be abolished by increasing the dose of insulin. The nature and site of action of the inhibitory substance or substances is at present unknown.

It is hoped that the recent work of Rabin and his coworkers in apparently separating the diabetogenic principle from the growth principle in pituitary extracts may yield information of value in this respect.

SUMMARY

In conclusion I should like to state that in my opinion the syndrome of diabetes mellitus is due to an imbalance between insulin and the pituitary-adrenal axis and thus may be caused by either failure to secrete insulin or the hyperfunction of the pituitary adrenal axis, although at present other factors cannot be eliminated.

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DISCUSSION

DR. FRANCIS D. W. LUKENS (*Philadelphia, Pa.*): There has been a great deal of interest in Dr. Bornstein's work, and it is a privilege to have him here and to learn of this at first hand. One cannot discuss all the technical details of these very difficult methods, but I might say that over the years, and with the stimulation that Dr. Best has given to many of us, a great many people have been trying to measure insulin in blood, and these efforts are constantly improving. This is at least a very important step forward, regardless of how much it may be refined in the future.

Whenever a new method is developed and whenever new facts are observed, our old ideas must be adjusted. Here is one thought that Dr. Bornstein's report gave me. Dr. Wrenshall has reported to this society on the fairly consistent low insulin content of the pancreas of young diabetics; supposedly it is a form of insulin-deficient diabetes. Drs. Falta, Himsworth, Lawrence and others have commented on the insulin sensitivity of young diabetics and have thought this might mean an insulin-deficient diabetes. If I understood him, Dr. Bornstein said that what may be called "zero insulin diabetics" (I must paraphrase him hastily) fall into all age groups. Will this force us to realign some of our present understanding? In any case Dr. Bornstein's experiments will stimulate our thinking considerably.

DR. J. BORNSTEIN, (*Closing*): I do not consider that Dr. Lukens need be quite so concerned about this apparent discrepancy, because in our study, we have unfortunately been able to study only three patients under the age of twenty. In these cases no insulin could be detected, and the plasma did not diminish the subsequent insulin sensitivity of the animals.

The other cases, in which a zero value for insulin was obtained, are only regarded as an apparent lack of insulin, as in all cases the insulin sensitivity of the test animals was diminished after the injection of the test plasma, and so I would interpret these findings as indicating that probably a large excess of inhibitory substance was probably present, and that this masks any insulin effect, although insulin may be present in such a sample of plasma.

Hormones and the Metabolism of Isolated Tissues

M. E. Krahl, Ph.D.

ST. LOUIS, MISSOURI

In diabetes there are disturbances in the utilization of glucose, in amino acid and protein metabolism and in the synthesis and breakdown of fat. The present brief review is confined to our own recent experiments on the first and second of these subjects. Experiments on the third topic, showing that fat synthesis from 2 carbon substances is deficient in diabetes, have appeared from two laboratories.[1, 3, 4]

GLUCOSE UTILIZATION BY STRIATED MUSCLE

The test object which we have employed in experiments on glucose utilization is the excised rat diaphragm. The diaphragm is carefully removed, washed and incubated for a definite time at 37°C. in a medium simulating extracellular fluid. Glucose uptake and other changes can be measured by analyses of aliquots of diphragm and medium before and after incubation.

INSULIN. Gemmill[6] showed that glucose use and glycogen formation by diaphragm are enhanced by addition of insulin to the medium in vitro, an observation later confirmed by many investigators.

Glucose use by diaphragm from severely diabetic (alloxan) rats is only 50 to 60 per cent of normal.[10, 16] Added insulin returns the rate toward normal (Figure 1).

These experiments indicate clearly that glucose utilization by a striated muscle can be increased by extra insulin and decreased in insulin deficiency. They supplement earlier experiments to the same end on whole and eviscerated animals and on perfused organs; the relation of these to the in vitro measurements has recently been reviewed,[5, 7, 8] the present experiments also provide the basis for a further study of the inhibitory factors against which insulin acts in increasing glucose uptake.

PITUITARY—ADRENAL CORTICAL FACTORS. Krahl and Park[11] observed that glucose uptake of diaphragms from hypophysectomized rats is higher than that of the normal, 4.9 mg. per gram per hour, as compared to a control rate of 3.5 (Figure 2). The maximum effect is reached about 15 to 20 days after operation. This has been repeatedly confirmed by new experiments of our own group[14] by Villee and Hastings[16] and by Bornstein and Nelson,[2] but not by Li, Kalman and Evans.[12] The reason for this discrepancy is not clear. Glucose uptake of diaphragms from adrenalectomized rats is slightly increased.[10, 16] But in no case is the effect from adrenalec-

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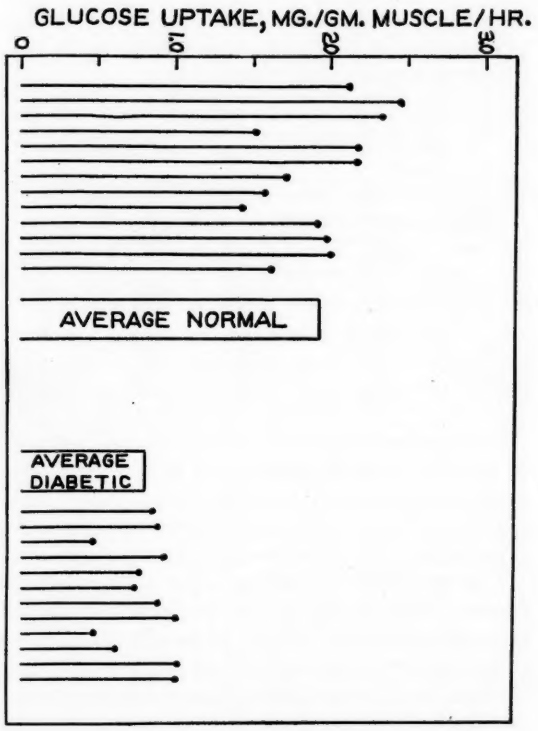

FIGURE 1 Glucose uptake by diaphragms from normal and severely diabetic (alloxan) rats. The muscle was shaken in oxygenated Krebs-bicarbonate solution and the medium analyzed for glucose before and after two hours of incubation at 37°C. The initial glucose concentration of the medium was 100 mg. per cent. From Cori (5) and Krahl (8)

tomy large enough to account for the increase in glucose uptake after hypophysectomy.

The isolated muscle of the hypophysectomized-adrenalectomized rat is still responsive to insulin, the glucose uptake being raised to a common level of about 7 mg. per gram per hour for the normal, for hypophysectomized, or for hypophysectomized-adrenalectomized cases. Hence the glucose uptake of muscle is in part under an insulin-reversible inhibitory influence from the pituitary and adrenals and in part under an inhibition which persists even when both these glands are removed.[11, 14, 15]

The nature of the inhibitory factor from the pituitary has now been extensively investigated with the diaphragm as test object.[13, 14] Partially purified anterior pituitary fractions, and even some samples of once crystallized growth hormone, produced significant depression of glucose uptake when injected into hypo-

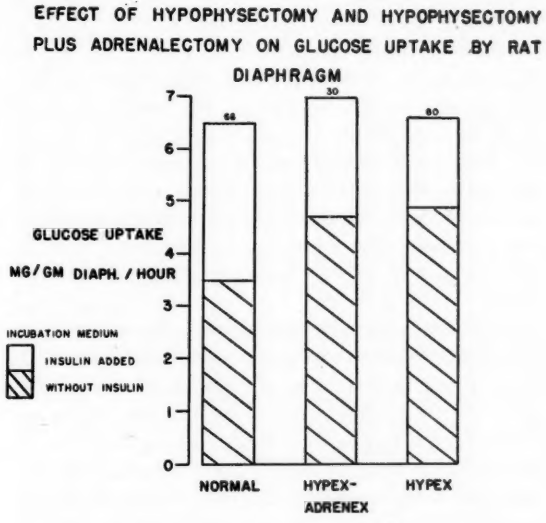

FIGURE 2 Effect of hypophysectomy and hypophysectomy plus adrenalectomy on glucose uptoke by rat diaphragm. The height of the cross-hatched area represents the rate without added insulin; the total height represents the rate with 0.1 unit per ml. of incubation fluid. The number of rats used is given at the top of each bar. From Krahl (8)

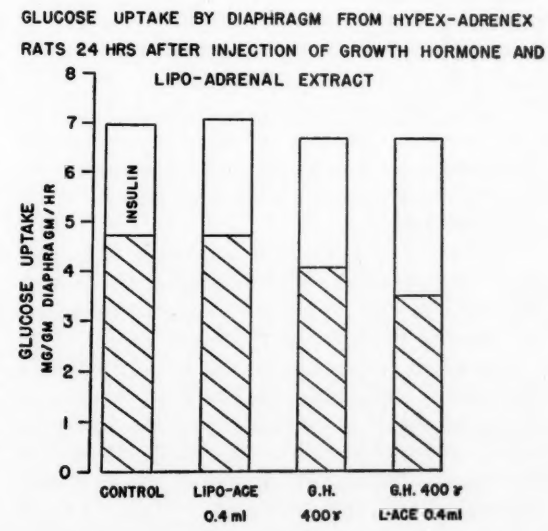
GLUCOSE UPTAKE BY DIAPHRAGM FROM HYPEX-ADRENEX RATS 24 HRS AFTER INJECTION OF GROWTH HORMONE AND LIPO-ADRENAL EXTRACT
GLUCOSE UPTAKE MG/GM DIAPHRAGM/HR
INSULIN
CONTROL
LIPO-ACE 0.4 ml
G.H. 400 γ
G.H. 400 γ L-ACE 0.4ml

FIGURE 3 Glucose uptake of diaphragms from hypophysectomized-adrenalectomized rats. The growth hormone was given intraperitoneally 24 hours, the lipo-adrenal extract in divided doses at 24 and 6 hours, prior to removal of diaphragms. For significance of cross-hatched and white areas, see Figure 2. From Krahl (8)

physectomized rats 3 hours before excision of the diaphragm. Four times crystallized growth hormone, on the other hand, was inactive at 3 hours, but active if given 24 hours to take effect; these highly purified samples were inactive at 3 hours even when large doses of adrenocorticotropic hormone were given concurrently.[8] This shows conclusively that growth hormone, as now prepared, does not account for all of the inhibitory activity of cruder pituitary extracts toward glucose uptake by muscle. The suggestion has been made that the inhibitor can be derived from growth hormone in the body.[8, 14]

Both growth hormone and adrenal cortical factors are involved in inhibition of glucose uptake by muscle.[13, 14] For example, in one series of experiments 400 micrograms of growth hormone lowered the rate of glucose uptake by diaphragms from hypophysectomized-adrenalectomized rats from a control value of 4.7 to 4.1 mg. per gram per hour; concurrent injection of lipo-adrenal extract (Upjohn) equivalent to 800 micrograms of compound E, a dose which was inactive alone, lowered the rate still further to 3.4 (Figure 3).

INSULIN AND PEPTIDE SYNTHESIS

Many experiments are available to show that insulin raises the rate of amino acid removal from plasma in whole or eviscerated animals. The experiments summarized here represent an attempt to follow the amino acids one step further and to determine their fate and the controlling factors in their disappearance.

Liver slices or diaphragms were incubated in a physiological medium containing radioactive glycine-1-C^{14} or phenylalanine-3-C^{14}; the radioactivity incorporated into the peptide glutathione and the total proteins of the tissue was measured.[9]

The results are expressed as counts per minute per mg. of the substance isolated. The higher the count incorporated under a given set of conditions, the greater the degree of synthesis, and vice versa.

Glutathione, containing the amino acids glutamic acid, cysteine, and glycine, was chosen for this purpose largely because it is the only typical simple peptide which can be readily isolated in crystalline form with high purity. Tissues from normal and from severely diabetic (alloxan) rats were used.

Diabetes reduces radioactive glycine incorporation into cuprous glutathione from a level of 3200 c.p.m. per mg. for normal liver to a level of 497 for diabetic liver. The values for protein fractions from normal and diabetic were: liver, 138 for normal, 19 for diabetic; diaphragm, 53 for normal, 21 for diabetic (Table 1).

Fasting alone (24 hours) results in rates of glycine incorporation which are intermediate between the normal non-fasting and the diabetic levels.

TABLE 1 Glycine-1-C^{14} incorporation into glutathione and protein fractions of liver and diaphragm from normal and diabetic rats. No glucose was added to the incubation medium.

Fraction Isolated	Insulin Added to Medium units per ml.	Radioactivity incorporated C.P.M. Per Mg. Normal, Non-Fasting	Normal, Fasting	Diabetic, Fasting
Liver Cuprous Glutathione	0	3208	1068	497
	0.1	3525	1097	—
Liver Protein	0	138	43	19
	0.1	127	41	—
Diaphragm Protein	0	53	33	21
	0.1	70	43	—

Similar experiments with phenylalanine-3-C^{14} instead of glycine-1-C^{14} gave: normal liver protein 160 c.p.m. per mg., diabetic 45; normal diaphragm protein 130, diabetic 20. Thus, the deficiency in uptake of radioactive amino acids is not confined to glycine.

This net decrease in labeled amino acid uptake in diabetes could be due to decreased peptide synthesis or to dilution, in the diabetic, of the glycine-1-C^{14} by a larger glycine pool; the larger pool might arise from increased protein breakdown. In an attempt to decide in a preliminary way between these two alternatives, new experiments with normal and diabetic liver were performed. Liver slices were incubated in medium containing forty times as much labeled glycine as in the initial experiments. At this higher glycine concentration, dilution of the radioactivity by unlabeled glycine from liver protein is much smaller than before. Therefore, incorporation of radioactivity into glutathione by normal and diabetic liver should be at rates much closer together than before if the difference between normal and diabetic which was initially observed were due solely to a larger pool of unlabeled glycine in the diabetic. Actually, it turns out that the relative reduction in glycine-1-C^{14} incorporation for the diabetic is 77 per cent at the higher glycine concentration as compared to 84 per cent at the lower. Since the reduction is nearly the same in the two cases, it must be concluded that the net decrease in amino acid uptake is attributable principally to decreased peptide synthesis in the diabetic tissues. A limited concurrent increase in protein breakdown in the diabetic is not excluded.

The question of the specific relation of insulin to rates of amino acid uptake by normal and diabetic tissues has been explored and found to be related to the availability in the medium of glucose as a substrate.

In all the experiments on amino acid uptake de-

scribed above, no glucose or other substrate was added to the incubation medium, the only glucose present being that carried over with the tissue. Under these circumstances, addition of insulin in vitro at a concentration of 0.1 unit per ml. produced no consistent increase in amino acid uptake by normal or diabetic tissues.

In another series of experiments carried out with 140 mg. per cent glucose in the medium, the cuprous glutathione isolated after incubation of diabetic liver was found to incorporate glycine-1-C^{14} to the extent of 1480 c.p.m. per mg.; with insulin present in vitro, the value was 2940 c.p.m. per mg. Hence, glucose alone raises the uptake in the diabetic from the value of 497 c.p.m. which was obtained without substrate. Insulin in vitro raises it still further, to a value very close to the mean normal level of 3200. A similar relationship to the availability of glucose and insulin was observed for the protein fractions of liver and diaphragm (Table 2).

Peptide synthesis in isolated tissues is thus correlated with glucose uptake in a general way. This finding is consistent with the requirement for energy-yielding metabolites of glucose in glutathione synthesis by a cell-free system.[17] Whether insulin influences peptide synthesis by a mechanism other than by stimulation of glucose uptake remains to be determined.

TABLE 2 Glycine-1-C^{14} incorporation into glutathione by liver slices from severely diabetic rats.

Concentration Glucose Added to Medium	Radioactivity incorporated C.P.M. Per Mg.	
	No Insulin Added to Medium	Insulin Added to Medium
mg. per cent		
0	632	598
140	1480	2940

SUMMARY

Glucose utilization by muscle is under at least two types of insulin-reversible inhibition.

One type of inhibititon is produced by a factor from the anterior pituitary gland which requires the concurrent presence of adrenal cortical products for full activity. This pituitary factor is closely related to growth hormone as now prepared, but apparently is not identical with it.

A second type of insulin-reversible inhibition is present even when both the pituitary and the adrenal glands have been removed. The chemical nature of this inhibition remains to be defined.

Incorporation of radioactive glycine into tissue glutathione and proteins is reduced in severe diabetes and enhanced by insulin in vitro in presence of glucose. The effect of insulin is apparently principally upon rate of peptide formation rather than upon rate of breakdown of proteins to their constituent amino acids.

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DISCUSSION

DR. F. D. W. LUKENS (*Philadelphia*). With the exception of Dr. Best's lecture, Dr. Krahl's paper is the only presentation of current work on the action of insulin, a topic of primary interest to this Association. He reminded us that insulin accelerates the utilization of carbohydrate by all three of the major pathways, namely, glycogen formation, fat formation and oxidation. If time permitted, he would have made a summary of other work in this field. Therefore, he may forgive me if I indicate in an oversimplified way three approaches to the study of the action of insulin which I find particularly thought-provoking. The first is the work of Drs. Krahl, Cori and their associates who have attempted to learn the biochemical site of action and to study the role of insulin inhibitors. The second is Dr. Levine's examination of the altered permeability of the cell to glucose under the influence of insulin. The third is the work of Dr. Stadie who has observed the binding of insulin to tissue and recently, with radioactive insulin, has begun to quantitate the relations between the amount of insulin bound to tissue, the glycogenic function of insulin so bound, and the effect of hormones and other inhibitors on both the binding and the glycogenic function.

As a result of this comment, one question occurs to me. Does the effect of insulin in the hypophysectomized-adrenalectomized rat mean that there is an inhibitor which persists in the absence of these glands? Might this not be an action of the increased dose of insulin on the permeabiliity to glucose or on the binding of insulin independent of any hypothetical inhibitor? Some of Stadie's results suggest that this may be more than a matter of semantics. Thus, with labeled insulin Stadie has found that the *binding* of insulin by the diaphram is the same in normal and hypophysectomized rats, although the insulin effect is greater in the hypophysectomized tissue. In other words, the insulin sensitivity of the hypophysectomized animal is here measured as a greater effect per unit of insulin bound. On the other hand, in examining the serum of insulin-resistant patients, this group finds a striking prevention of the binding of radio-insulin. In summary, I suppose that the assumption of inhibitors is made with due regard for possible future developments.

Another point which prompts an attempt at correlation is this. We showed that in Houssay animals, in the absence of insulin, growth hormone had no effect on nitrogen retention. Dr. Krahl's experiment showing that amino acids are not incorporated by tissue in the absence of glucose even when insulin is present is a thought-provoking companion experiment. It looks as if protein anabolism by muscle were dependent on the system insulin plus glucose much as the metabolism of the brain is dependent on the system oxygen plus glucose.

DR. CHARLES H. BEST: (*Toronto*) I wonder if Dr. Krahl would review again the data I heard him give elsewhere on how long he thinks insulin may persist after cessation of dosage or removal of the pancreas.

DR. M. E. KRAHL (*closing*): With respect to Dr. Lukens' question about inhibitors, what I should have said, perhaps, was that there is a limitation in glucose uptake which persists after the hypophysis and adrenals are removed. I shall be very much interested in seeing how the experiments which Dr. Levine and others are conducting finally turn out in this respect.

With respect to Dr. Best's question, it has been our experience, that if one uses rats which have received alloxan, it is very difficult to demonstrate a reduced glucose uptake or a reduced amino acid uptake unless, first, the rats have been given very large doses of alloxan so that they have become maximally diabetic and, second, these animals have been kept for at least five to seven days after the alloxan injections, or after insulin treatment has been withdrawn.

Detection of Mild Diabetes Mellitus By Feeding Glucose To Induce Glycosuria

P. H. Futcher, M.D. and G. Sauvé, M.D.

BALTIMORE, MARYLAND

Many physicians have recognized that mild diabetes may not be apparent if tests are made when the subjects are in the fasting state. In screening for diabetes there is, therefore, an advantage in imposing a load upon the carbohydrate metabolism to demonstrate abnormalities. During the performance of diagnostic studies on ambulatory patients, we have given 75 gm. of glucose and looked for glycosuria. When reducing substances were found in the urine, the possible presence of mild diabetes was further explored additional technics. We have attempted to evaluate , as indicators of the presence of mild diabetes, the relative helpfulness of this procedure and the frequently employed routine of securing tests of the fasting blood sugar and urine sugar.

From the Department of Medicine, Johns Hopkins Medical School and Hospital. Dr. Sauvé held a fellowship in the Private Outpatient Service during the conduct of this investigation.

The authors are grateful to Drs. Russell H. Wilder and John E. Howard for suggestions regarding possible screening procedures offered while this study was being planned and to Dr. Elihu S. Wing for assistance in the tabulation of the results. Dr. F. W. Barnes Jr. was kind enough to read the manuscript.

Address communications to Dr. Futcher, The Johns Hopkins Hospital, Baltimore 5, Maryland.

OUTLINE OF TECHNICAL PROCEDURES

General Plan of Study: The usual procedure was to give the experimental screening test for diabetes on the first day of study; to have tests of blood and urine before breakfast the following morning; and, in selected cases, a glucose tolerance test within the next week. The tolerance test was performed on subjects who had shown a positive screening test, particularly those who excreted a large amount of reducing substance in the urine. Exceptions to the usual procedures were made in certain cases.

Subjects: The 1000 subjects were selected from a group of ambulatory adult patients on the upper economic levels undergoing diagnostic surveys in the Private Outpatient Service of the Johns Hopkins Hospital for a variety of complaints during the period December, 1949, through November, 1951. The great majority were

white. Those selected included both sexes; save in rare instances they were over 40 years of age; in no instance had been previously recognized to suffer from diabetes; and manifested no striking symptoms of the disease. While the group did not include all patients over 40 admitted to the clinic for diagnostic study during the period in question, we can find no evidence of special selection on the basis of the clinical history or physical findings save in the case of the few subjects under the age of 40. Some in this latter group were selected for the test because of a family history of diabetes. The records of all subjects, in whom the diabetic screening test was found positive and who were subsequently evaluated by a glucose tolerance test, have been reviewed for evidence of factors other than diabetes which might cause impairment of carbohydrate metabolism; none of the group gave evidence of a recent marked restriction of caloric intake, liver disease or thyroid, adrenal or pituitary disease.

The 1000 screening tests for diabetes reported upon, represent tests on 1000 different subjects and have been selected from the first 1008 such tests performed. The 8 tests have been excluded from our report for various reasons. Three of them represented a repetition of a previous test on 3 subjects. Two of them were performed on patients previously demonstrated to have diabetes mellitus. Two of the tests were performed on patients demonstrated to suffer from pentosuria and renal glycosuria. In another test the reduction of the Benedict's solution was reported "atypical"; the patient was not further studied.

Conduct of the diabetic screening test: The test was administered to the majority of the subjects in the early afternoon. Most of them had eaten nothing since breakfast. After each subject had emptied his bladder, he drank a solution containing glucose (75 gm. dissolved in 400 ml. of water flavored with lemon juice) during the course of a few minutes. The urine collected two and one-half hours later was tested for reducing substance by Benedict's method. Subjects were instructed not to eat anything until the test was completed; no control of the intake of water was imposed before or during the test.

Technic for determination of urinary glucose: On the same day that the specimen was voided, to a test tube were added approximately 5 ml. of qualitative Benedict's solution (National Formulary) and 8 drops of urine. It is estimated that the amount of urine added varied roughly in the range 0.2 to 0.4 cc., depending on the orifice of the dropper employed. In rare instances the tube was heated over an open flame for two minutes; usually it was immersed in a boiling water bath for 5 minutes. Immediately after heating, the color of the solution was observed and the test reported as "negative", or as "positive" to various degrees—"Tr." (trace, very slight reduction giving a greenish tinge), "1+," "2+", "3+", or "4+", the final term indicating complete reduction.

Conduct of glucose tolerance tests: Tests for sugar in the urine were made by Benedict's method and all blood sugar measurements reported in our study by the Folin-Wu copper reagent[1] after tungstic acid precipitation. In the performance of the glucose tolerance test 100 gm. of glucose and 400 ml. of water were given. Venous blood was used for blood sugar determinations.

RESULTS

General: Of 1000 screening tests conducted on 1000 subjects, 809 revealed no evidence of reduction of Benedict's solution and were termed "negative" (Group O, Table 1). The urine of 191 subjects contained amounts of reducing substance varying from a trace to 4+ after the ingestion of 75 gm. of glucose. Some of these 191 subjects found it inconvenient to prolong their diagnostic study by remaining for the performance of a glucose tolerance test, and often no invitation to do so was extended by the hospital staff to those manifesting only traces of reducing substance in the urine. Hence, there was evaluated with a glucose tolerance test a relatively higher proportion of subjects manifesting heavy "glycosuria" than of subjects manifesting lesser degrees of "glycosuria." The discussion below concerns itself essentially only with those 70 subjects manifesting positive screening tests in whom the possible presence of disordered carbohydrate metabolism has been evaluated with the aid of a glucose tolerance test or, in 6 instances, the fasting blood sugar test alone. The findings on the 1000 subjects are summarized in Table 1.

Criteria for evaluating abnormal carbohydrate metabolism: We have regarded as abnormal a fasting blood sugar which exceeds 120 mg. per 100 cc. In evaluating the results of the glucose tolerance test, we have regarded as suspicious of deranged metabolism those instances in which the blood sugar level at 2 hours exceeded 119[2] and as definitely abnormal those in which the 2 hour level exceeded 139.[3, 4]

Classification of patients manifesting positive screening tests for diabetes: The subjects manifesting reducing sub-

TABLE 1 Screening Tests for Diabetes

Designation of group	Significance of group	Total number in group	Number subjects with indicated degree of reduction of Benedict's solution: Trace	+	++	+++	++++
0	Negative screening test	809	0	0	0	0	0
1	Positive, not studied	121	50 41*	41 34	20 17	7 6	3 2
2	"False positive screening test"	21	5 24	4 19	4 24	4 19	3 14
3	Diabetes?: screening test not strategic†	18	1 5	3 17	2 11	4 22	8 45
4	Diabetes?: screening test strategic‡	31	3 10	6 19	9 29	8 26	5 16

* Underscored figures indicate proportion of group represented by figure immediately above, expressed as per cent.
† Subjects with elevated fasting blood sugar and/or glycosuria when fasting.
‡ Subjects with normal fasting blood sugar and no glycosuria when fasting. See Table 2 for glucose tolerance test.

TABLE 2 Glucose Tolerance Tests

Results on the 31 subjects in group 4, in whom the screening test was strategic to recognition of possible diabetes.

Subject	Age	Sex	Screening Test	Glucose Tolerance Test: Fasting		½ hour		1 hour		2 hour		3 hour	
	yrs.			Blood sugar	Urine sugar	Blood sugar	Urine sugar	Blood sugar	Urine sugar	Blood sugar	Urine sugar	Blood sugar	Urine sugar
1	63	M	2+	100	—	158	—	245	4+	164	2+	120	—
2	63	F	Tr.	96	—	168	—	215	—	200	—	120	2+
3	47	F	2+	92	—	208	—	194	—	140	—	120	—
4	58	F	1+	92	—	220	*	208	*	176	*	130	*
5	34	M	3+	100	—	190	—	234	3+	178	3+	122	Tr.
6	42	M	Tr.	100	—	178	—	214	—	214	1+	142	1+
7	63	M	1+	112	—	190	—	270	2+	200	3+	132	2+
8	40	M	4+	84	—	190	—	270	Tr.	220	4+	168	4+
9	62	M	4+	94	—	184	—	224	—	224	—	144	—
10	64	M	2+	138†	—	244	—	318	4+	238	4+	128	4+
11	43	F	3+	88	—	208	—	196	1+	158	3+	122	2+
12	56	M	4+	128†	—	200	—	244	Tr.	200	2+	124	—
13	55	M	3+	100	—	220	—	236	2+	188	2+	80	1+
14	47	M	3+	108	—	234	Tr.	255	3+	184	4+	60	Tr.
15	54	F	1+	92	—	184	—	184	—	168	—	98	—
16	56	M	3+	100	—	173	—	190	—	208	2+	84	—
17	65	M	1+	88	—	182	—	168	—	144	—	54	—
18	37	F	1+	120†	—	170	—	204	2+	152	—	60	—
19	59	M	3+	114	—	176	—	204	2+	176	3+	60	Tr.
20	55	F	3+	96	—	162	—	162	Tr.	158	—	117	—
21	53	M	2+	108	—	176	1+	159	—	152	—	84	—
22	58	M	4+	114	—	114	—	260	1+	230	4+	80	1+
23	51	M	2+	104	—	196	—	200	3+	162	4+	50	2+
24	55	F	1+	108	—	188	—	164	—	144	—	88	—
25	31	M	2+	104	—	274	1+	192	4+	148	Tr.	68	—
26	43	M	2+	100	—	208	—	152	2+	124	—	76	—
27	34	F	2+	80	—	142	—	162	—	132	—	108	—
28	53	M	Tr.	128†	—	264	—	182	2+	138	—	80	—
29	57	M	4+	94	—	164	—	182	Tr.	124	1+	54	Tr.
30	48	M	3+	104	—	159	—	164	—	128	—	68	—
31	51	M	2+	114	—	200	—	188	Tr.	128	—	56	—

* Data not available.
† Fasting blood sugar measured a few days previously was 108 mgm.% in Subject 10, 120 in Subject 12, 108 in Subject 18, and 120 in Subject 28.

stance in the urine during the screening tests have been divided into 4 groups in an attempt to determine the effectiveness of the test as an indicator of the presence of mild diabetes mellitus (Table 1).

Group 1 includes the 121 subjects who were not evaluated with a glucose tolerance test. The fasting blood sugar of 6 of these subjects was not measured. In 4 of the subjects the fasting blood sugar ranged from 124 to 132. In the remainder of the subjects the fasting blood sugar was below 121. Only 2 of the group of 121 excreted reducing substance in the fasting urine.

Group 2 includes 21 subjects, who, when subjected to a glucose tolerance test manifested a 2 hour blood sugar level below 120. These 21 patients have been characterized as manifesting "false positive" screening tests in so far as evidence of diabetes demonstrated by the glucose tolerance test is concerned. In the 16 subjects in this group in whom the routine measurement of the fasting blood sugar was made the level did not exceed 120. None of the 21 excreted sugar in the fasting urine.

Group 3 includes 18 subjects who, in addition to manifesting a positive screening test also manifested an initial fasting blood sugar in excess of 120 and, in 3 instances, reducing substance in the fasting urine. In 6 instances a tentative diagnosis at least of diabetes was established by a fasting blood sugar in excess of 139, and in 12 by the finding during a glucose tolerance test of 2 hour blood levels which exceeded this same figure. This group thus is constituted of those patients tentatively demonstrated to have diabetes in whom the possibility of the existence of the disease was initially raised by standard procedures (fasting blood sugar determination and urinalysis) as well as by the diabetes screening test.

Group 4 (Table 2) includes 31 subjects. The fasting urine was examined in 30 of the group and in no instance contained glucose. In none of the 31 was the initial fasting blood sugar in excess of 120. Subsequent to the finding of a positive screening test, all 31 patients manifested various degrees of abnormality during a glucose tolerance test. The subjects listed at the top of Table 2 are those in this group with the relatively more severe derangement of carbohydrate metabolism. Thus in Subjects 1 through 12 the blood sugar after 3 hours exceeded 119; this was not the case with Subjects 13 through 25, in whom the 2 hour blood sugar was in excess of 139, however. In Subjects 26 through 31 the 2 hour level was only slightly in excess of 119. In these 31 subjects the possible impairment of glucose metabolism was recognized only because a positive screening test led to study by a glucose tolerance test.

Significance of degree of "glycosuria" during a screening test for diabetes: Table 1 presents the frequency with which various amounts of reducing substance were found during the screening test in the 191 subjects manifesting positive tests. Several subjects with weakly positive screening tests were subsequently found to fall into categories (Groups 3 and 4) characterized by abnormal glucose tolerance tests.

Variability of presence of reducing substance in urine following ingestion of glucose: Of the 70 subjects in Groups 2, 3, and 4, (all of whom excreted reducing substance in the urine during the screening test,) 63 provided additional urine specimens for analysis during a glucose tolerance test performed a few days later. In 15 of 21 subjects in Group 2; none of 12 in Group 3; and 7 of 30 in Group 4 thus re-examined failed to excrete reducing substance detectable by Benedict's solution.

Age of subjects in each group: The average ages of the subjects in Groups 1, 2, 3, and 4 were 50, 50, 55, 50 years respectively. In each group the number of subjects whose ages exceeded the mean approximately equalled the number of those whose ages were less than the mean. There was a predominance of females in all 4 groups.

COMMENT

A strikingly high proportion (191 out of 1000) of these subjects chosen preponderantly from the middle and later decades of life, excreted reducing substance in the urine during the diabetes screening test.

Since only 70 of the 191 in question were further investigated for other evidence of possible deranged carbohydrate metabolism, no conclusion can be drawn as to the nature of the reducing substance in many instances. That the 49 subjects in Groups 3 and 4 were suspected of having at least a minimal impairment of carbohydrate metabolism, suggests a significantly high incidence of metabolic disorder in the group of 1000. The incidence would almost certainly have been demonstrated to be higher had we investigated the remaining 121 subjects with positive screening tests. (Group 1). Exactly how many of the subjects with possible impairment of carbohydrate metabolism should be characterized as suffering from diabetes mellitus is a question depending on the widely debated problem of the interpretation of a glucose tolerance test. It seems likely that, of the 18 subjects in Group 3 and the first 25 in Group 4, many suffered from true diabetes mellitus of at least a

mild degree of severity.[4] Subsequent observation of these subjects will be necessary to confirm the presence of the disease.

Whether one is justified in regarding this incidence of possible metabolic abnormality as characteristic of the general population of the United States over 40 years of age is uncertain. At least two factors were active in the selection of these patients before they applied to our hospital for care. One influence, probably tending to increase the expected incidence of discoverable metabolic abnormality, was the fact that the majority of these patients had an illness which caused them to seek medical care. Another influence, which might decrease the incidence of discoverable abnormality, was the fact that many of our patients had recently been examined by their physicians at home before coming to our hospital and no evidence of diabetes had been reported to them.

Of the total of 49 subjects with possible impairment of carbohydrate metabolism (Groups 3 and 4), in 31 (Group 4) the impairment was revealed by the finding of a positive screening test; it would have escaped detection had one relied only on the history, the fasting blood sugar and fasting urinalysis. Thus the screening test contributed significantly to the recognition of a possible metabolic abnormality in 3 per cent of the 1000 subjects in whom it was applied; it seems likely that derangement could have been demonstrated in others manifesting positive screening tests (Group 1) had they been further studied.

Of the 70 subjects manifesting positive screening tests and in whom there was additional evidence sufficient to afford an evaluation of the metabolism of carbohydrate, 21 (Group 2) were demonstrated to show a normal glucose tolerance test. Thus, 30 percent of the screening tests so evaluated were "false positives". These 21 subjects in Group 2 constituted 40 per cent of the 52 subjects in Group 2 and 4; none of the subjects in these 2 groups in whom the determinations were made manifested evaluation of the fasting blood sugar or fasting glycosuria. Since there was a tendency to pick for further evaluation with a glucose tolerance test those subjects manifesting the heavier concentrations of urinary reducing substance during the screening test, selection was in favor of studying those subjects likely to have greater derangement of carbohydrate metabolism than was present in those manifesting weakly positive screening tests. Hence it is likely that the incidence of "false positives" would be greater than 40 per cent in the 121 patients in Group 1, who were not further studied.

The known variation in renal threshold for sugar from subject to subject furnishes a likely explanation for some of the instances in which reducing substance appeared in the urine during a screening test despite the presence of ostensibly unimpaired ability to metabolize glucose, as indicated subsequently by a normal glucose tolerance test. The observation of a 2 hour blood sugar level below 120 during a tolerance test, our possibly arbitrary criterion for "normal carbohydrate metabolism", does not obviate the likely possibility that soon after the ingestion of glucose the level of blood sugar may have exceeded the renal threshold. Hence, the level of the peak of the blood sugar curve, as well as the duration of its elevation, might be expected to influence the appearance of glycosuria and hence the result of the screening test. In some instances the excretion of non-glucose reducing substances probably resulted in a positive screening test.[5]

More difficult to explain is our frequent failure to observe glycosuria during a glucose tolerance test performed subsequent to a positive screening test. This failure occurred in 22 of the 51 subjects in Groups 2 and 4 on whom data are available, or 43 per cent. It seems unlikely that this inconsistency can be completely explained by the presence of such variables as divergencies in the rate of excretion of water and variations in the proportions of urine and Benedict's solution employed during the analytical procedure. Since the screening test was often performed on the first day that the subjects visited the hospital, it seems likely that they were under greater tension at that time than during the performance of the glucose tolerance test a few days later. That emotional tension in nondiabetic subjects may be accompanied by post prandial blood sugar levels higher than those encountered during periods of greater composure has been reported by Diethelm[6]; conceivably such tension may have elevated the blood sugar in some of our subjects and therefore have contributed to the fleeting excretion of reducing substance which we sometimes observed. The glycosuria reported by some observers as an accompaniment of emotional tension in normal subjects has been tentatively ascribed by Mirsky[7] to renal influences rather than to hyperglycemia. The variability of glycosuria during the repeated conduct of a diabetic screening procedure in the same subject has been commented on by others.[8] All 12 subjects in Group 3 who were examined with a glucose tolerance test excreted reducing substance during the test; in general, the disorder of carbohydrate metabolism in Group 3 appeared more severe than that in Group 4.

To summarize our experience with the screening test, we found that in the group of 1000 subjects it was

instrumental in the recognition of possible impairment of carbohydrate metabolism in 31 who manifested no elevation of the initial fasting blood sugar and no fasting glycosuria. It was easy to supervise. The necessary analytical procedure was simple. We have not regarded the exact duration of the interval over which the urine was collected (usually two and one-half hours) as crucial; hence it has been possible for subjects to leave the laboratory area during the test for the performance of other examinations without the fear that a brief deferment of the recommended time of return to the laboratory will invalidate the results of the screening test. A definite disadvantage has been the occurrence of "false positive" results. We have no information on possible abnormalities in metabolism existing in the 809 subjects in whom the screening test was negative; despite the normal fasting blood sugar and the absence of glycosuria observed in the great majority of these 809 subjects, it seems likely that some of them suffered from mild impairment of carbohydrate metabolism which the screening test failed to demonstrate.[9]

Any screening procedure is necessarily a compromise. Factors governing evaluation of the compromise are the sensitivity and specificity of the test, its cost, and miscellaneous administrative and related factors in the environment. In the setting in which we employed it, the screening test had merit. It is our present plan to administer an abbreviated glucose tolerance test to those patients manifesting a positive screening test in which the reduction of the Benedict's solution is observed to be more than a trace; further study of patients excreting only trace amounts of reducing substance postprandially has been found unrewarding in the diabetic screening experience of others.[9] Glucose (100 gm.) will be fed and a single venous Folin-Wu blood sugar determination and urinalysis conducted 2 hours afterwards. Elevation of this blood sugar value above 119 will be regarded as evidence of possible impairment of carbohydrate metabolism and elevation above 139 as evidence of probable impairment. We shall continue to measure the fasting blood sugar at some time during the course of the diagnostic study. We would prefer to substitute for the screening test a measurement of the blood sugar 2 hours after the ingestion of glucose in all patients, if the clinic routine permitted the convenient adoption of such a screening technique. It is to be noted, however, that as with the screening test using a urinalysis, a screening procedure for diabetes involving the postprandial measurement of blood sugar has been reported to give indications of impaired carbohydrate metabolism which frequently cannot be substantiated by subsequent blood sugar determinations.[8]

Patients manifesting mild impairment of carbohydrate metabolism revealed by the screening test and subsequently confirmed by a glucose tolerance test have been told of the evidence of at least transitory impairment. Those who are obese have been instructed to lose weight. All have been advised to have examination of the blood and urine in the succeeding months and years for evidence of more pronounced impairment.

SUMMARY

An attempt has been made to discover mild diabetes mellitus by feeding glucose to induce glycosuria.

Studies were made of 1000 ambulatory patients not previously suspected of suffering from diabetes mellitus; with rare exceptions the subjects were over 40 years of age.

The urine of 191 of these patients, voided two and one half hours after the ingestion of 75 gm. of glucose, reduced Benedict's solution.

Additional studies, including glucose tolerance tests, sufficient to elucidate the possible presence of an impairment of glucose metabolism, were performed on 70 of these 191 subjects.

In 31 of these 191 subjects there were demonstrated varying degrees of impairment of carbohydrate metabolism which would not have been recognized had the studies been limited to examination of the fasting urine and measurement of the fasting blood.

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Mass Screening for Diabetes

The Use of a Device for the Collection of Dried Urine Specimens and Testing for Sugar [St. Louis Dreypak]

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The work of Wilkerson and his associates in the U.S. Public Health Service,[1] MacBryde,[2] Sharkey,[3] and others[4] support the belief long held in the minds of students of diabetes that the number of cases unknown to physicians probably equals the number diagnosed. Early diagnosis is desirable to control the progress of the disease and to prevent serious complications. The medical practitioner and the public health officer must accept the challenge presented by this situation.

From the St. Louis Clinical Diabetes Society. The work reported was made possible through the assistance of many members of the Society, and the St. Louis Retail Druggists' Association. The blood sugar tests were done in the laboratories of the Barnes, Firmin Desloge and Jewish Hospitals. Venous blood was collected in Vacutainers, courtesy of Becton-Dickinson Company. The authors acknowledge this aid with appreciation. This work was financed by the St. Louis Diabetes Association.

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SELECTION OF METHODS FOR DIABETES SURVEY

To find the cases of unknown diabetes one can undertake an initial examination of urine and then a blood sugar test if glycosuria is found. An alternative is to make blood sugar examinations routinely. Choice of the method must be determined by the number of people to be surveyed, their geographical situation, the laboratory facilities available, and the number of examiners on hand. Since the examination of urine is simple, requiring little apparatus, it seemed to us the preferable initial step especially since at least one hundred individuals must be checked to find a single case of undiagnosed diabetes. To make an impression on the problem, millions of individual urine or blood samples must be examined. Obviously, the initial urine examination would be simpler to carry out.

The objection to using the urine as the first step in a screening process lies in the fact that a negative blood test does not always exclude hyperglycemia. It is our belief, however, that there are few untreated diabetics

who will fail to show glycosuria if the urine is tested an hour after a meal containing a large amount of starch and sugar. Harting and Glenn[1] investigated the relative value of urine and blood sugar determinations in a survey conducted in Brookline, Mass. They concluded that a routine blood sugar test was a more reliable guide, especially in the instances where the blood sugar was elevated but not sufficiently to cause glycosuria. Here the diagnosis of diabetes may be in doubt even when a glucose tolerance test is made. One must grant that routine blood sugar tests will increase the fineness of the screening technic, but full time workers and a chemical laboratory are required. Furthermore, blood samples are much more difficult to obtain than urine samples. Our plan of procedure is so simple and inexpensive that the busy physician can effectively conduct a detection survey.

THE PROBLEMS OF MASS TESTING OF URINE SPECIMENS

Probably the reason that methods other than mass testing of urine have been advocated is because urine must be tested within a few hours after it has been voided, and a fluidtight container is required to transport specimens. Drey[5] was impressed with these facts and designed a container to carry urine dried on filter paper impregnated with sodium flouride. We have demonstrated that the drying of urine does not result in loss of sugar. The popularity of the technic is justified because, along with other reasons, it is not likely to give falsely positive results.

Drying biological materials on filter paper for preservation or for transportation is not new. Noguchi[6] in 1910 dried complement, amboceptor and antigen on filter paper for both the preservation of the material and to simplify the quantitative measurement of materials in performing serum tests for syphilis. Bronfenbrenner[7] supplied the Belgian Army with anti-sheep amboceptor dried on filter paper during World War I.

THE ST. LOUIS DREYPAK

The St. Louis Dreypak is the name given to a device for the collection and testing of dried urine specimens. A strip of coarse filter paper, ⅜ in. wide is sewn to a piece of polyethylene film. The filter paper is prepared by soaking it in a one per cent solution of sodium floride, and drying. A strip of stiff paper, 4½ in. by 1¼ in., is sewn to the other side of the plastic material. On it is written information regarding the subject. After testing, this portion is kept for the tabulation of data.

To prepare for testing, the strip is quickly dipped into urine and allowed to dry. Experiments have shown that the dried sugar is preserved for as long as 90 days. The plastic portion of the strip has a double purpose. It permits the immersion of the filter paper in boiling Benedict's qualitative reagent while limiting the extent of the chemical reaction, thus giving a roughly quantitative result. It allows the testing of the strips in packs of 20 to 30; each filter paper separated from its neighbor by the plastic.

The kit used in surveys here reported consisted of the strip inserted in an envelope along with an instruction sheet. The individual submitting the specimen was asked to address the envelope to himself; this saved secretarial work and insured the sending of a report to each person. The important item in the detailed instructions concerned the emphasis on collection of the urine to be tested within one to two hours after a heavy evening meal containing plenty of available carbohydrate; when tests are made on specimens obtained under these circumstances, there is increased liklihood of finding elevated postprandial blood sugar and glycosuria.

DISTRIBUTION AND COLLECTION

Since the U. S. Post Office Department has not issued permission for the mailing of dried urine specimens, other methods of distribution and collection were necessary. Some were distributed by druggists who were public service minded. One of us (N. W. D.) undertook the distribution to four industrial concerns; workers were instructed to take home a kit for each member of the family. Our hope was to reach both the older and younger members. The success of this procedure will appear later.

TECHNIC OF THE TEST

The strips are removed from the envelopes and are gathered together in packs of 20 to 30. They are held by a plastic clothespin and suspended for one minute in a pan of boiling Benedict's qualitative reagent. Glycosuria is shown by the appearance of a color on the filter paper similar to that shown by Benedict's test in the test tube. A strip showing the color change of a positive test will cause gross contamination of neighboring strips when it has been exposed to urine containing a large amount of sugar (3 per cent or more).

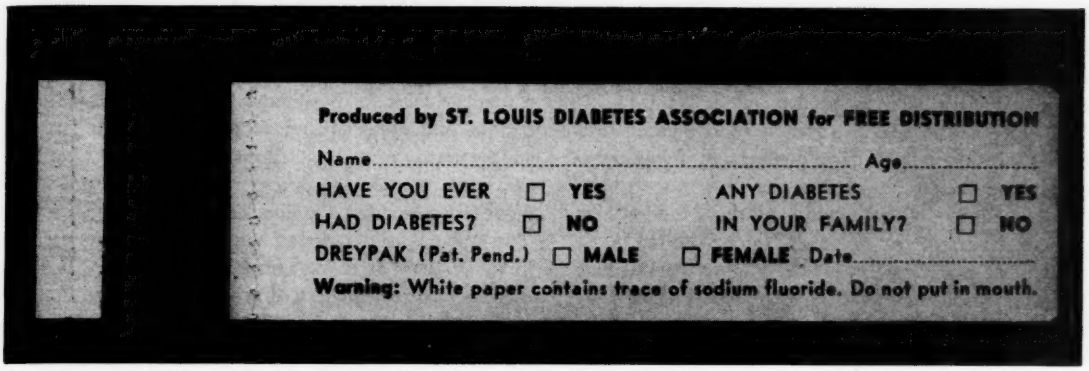
Produced by ST. LOUIS DIABETES ASSOCIATION for FREE DISTRIBUTION
Name..... Age.....
HAVE YOU EVER ☐ YES
HAD DIABETES? ☐ NO
ANY DIABETES ☐ YES
IN YOUR FAMILY? ☐ NO
DREYPAK (Pat. Pend.) ☐ MALE ☐ FEMALE Date.....
Warning: White paper contains trace of sodium fluoride. Do not put in mouth.

FIGURE 1. The St. Louis Dreypak testing strip with its attached information blank, which was distributed to the public with the following instructions:

1. WRITE PLAINLY your name and address on the envelope.
2. Also write your name on the strip. Answer the questions on the strip.
3. Eat a big meal. At least two slices of bread, potatoes and a sweet dessert in addition to other foods you want.
4. One to two hours after this meal, pass urine into a CLEAN pan or jar.
5. Dip the plastic end of the strip of paper QUICKLY into the urine and out again. Just wet the small bit of white paper attached to the plastic, that is all that is needed.
6. Place the strip on a piece of toilet paper, the paper side up. LET IT DRY OVERNIGHT.
7. After the strip is dry put it into the envelope and turn in the flap.
8. Return the envelope to the drug store where you got it, or other collection point. DO NOT MAIL.
9. A report of your test will be mailed to you.

An examiner quickly learns to detect contamination in negative strips adjacent to a highly positive strip. A team of four volunteer workers plus one doctor or technician can examine more than 1000 tests per hour. Two or three persons on such a team are needed to open envelopes and number the strips and envelopes to make sure of the accurate identification of positive tests.

DISTRIBUTION AND RETURN OF TESTING MATERIALS

Through the agency of 270 drug stores, 41,500 kits were distributed to the general public of St. Louis in 1950. Of this number, 5,087 strips were returned for tests—12 per cent of those distributed. In addition, the employees of four industrial concerns took 13,000 kits and returned 1,923—14.8 per cent.

INCIDENCE OF GLYCOSURIA

Of the 5,087 strips collected through drug stores, 391 (7.7 per cent) gave positive tests for sugar. Of the 1,923 collected from workers' families, 68 were positive (3.5 per cent). The higher rate of glycosuria in strips returned from the general public can probably be explained by the tendency of persons susceptible to diabetes to cooperate more readily. This group probably included many individuals with a family history of diabetes. Diabetes is five times more prevalent in relatives of diabetics than in the general population.

In 1948, when 17,000 specimens were examined, 10 per cent of the first thousand showed glycosuria. As the campaign progressed, the percentage dropped until in the last 5,000 specimens only 2 per cent were found positive. In 1949, 3,400 specimens were collected and the percentage showing glycosuria was 6. One can conclude that at the beginning of a diabetes detection campaign, the discovery of glycosuria would be relatively frequent. Many diabetics and persons predisposed to the disease submit specimens for examination early. Later, one finds that the incidence of glycosuria decreases to 2 to 4 per cent.

AGE AND SEX INCIDENCE

The age distribution of the persons submitting specimens is shown in Table 1. In the juvenile and young adult group (up to 30 years of age) there were 24

TABLE 1 The Age and Sex of the Population Sampled in 1950 Diabetes Case Finding Campaign

AGE	MALE		FEMALE		TOTAL	
	Number	Percent	Number	Percent	Number	Percent
1 to 29	755	11.5	846	12.9	1601	24.4
30 to 49	1059	16.2	1325	20.2	2384	36.4
50 and above	1010	15.4	1557	23.8	2567	39.2
Totals	2824	43.1	3728	56.9	6552	100.00

per cent, in the mature adult group (from 30 to 50 years), 36 per cent and in the older group (from 50 years upward), 39 per cent. Mature adults and older people, especially women, predominated.

In Table 2, the age distribution of the population of St. Louis is compared. The percentages in the three age groups was 50, 30, and 19 per cent, respectively. It was found, too, that the sex distribution differed. Of the persons in the 30 to 50 age group having tests, 24 per cent were women; while only 10 per cent of the general population in this age group are women. In other words, women showed greater interest in the tests than men; older people more interest than young people.

TABLE 2 The Age and Sex of the Population Sampled in the 1950 Case Finding Campaign Compared with the Distribution of the Total Population in St. Louis

AGE	MALE		FEMALE		TOTAL	
	Population Distribution Percent	Case Finding Campaigns Percent	Population Distribution Percent	Case Finding Campaigns Percent	Population Distribution Percent	Case Finding Campaigns Percent
1 to 29	24.5	11.5	26.0	12.9	50.5	24.4
30 to 49	14.7	16.2	15.5	20.2	30.2	36.3
50 and above	9.5	15.4	9.9	23.8	19.4	39.2

BLOOD SUGAR TESTS

An invitation to submit to a blood sugar test was extended to all persons who had positive tests for glycosuria; 61 per cent accepted. The tests were made one hour after eating a noon meal including potatoes, bread and a sweet dessert. The results are shown in Table 3.

TABLE 3 Results of blood tests made one hour after a heavy meal in 280 cases of 459 in which glycosuria had been found

Mg. Per 100 cc.*	Individuals Said to be Diabetic	Individuals Unaware of Diabetes
Under 120	8	137
120 to 149	6	17
150 to 199	9	17
200 to 299	31	27
300 and above	14	14
Totals	68	212

* Shaffer-Hartman Somogyi True Blood Sugar Method. Upper limit of normal 120 (9.10) corresponding to 130-150 by methods which do not determine true glucose.

Of 280 individuals who had glycosuria, 145 had postprandial blood sugar values less than 120 mg. per 100 cc., which strongly indicates that the glycosuria was nondiabetic or transitory. On the other hand, 135 persons had blood sugar values ranging from 120 to 400 mg.

A diagnosis of diabetes should not be made on the basis of one blood sugar determination, but in a campaign directed to the discovery of undiagnosed diabetes we can justifiably classify as diabetic those cases in which the value for postprandial to glucose is over 200 and as probable diabetics those in which the values are between 120 and 200. Among this latter group are the cases in which a glucose tolerance test is usually required to establish the diagnosis of mild diabetes.

In Table 4 is a statistical summary of the experience in the diabetes detection campaigns in St. Louis during the past three years: 1948, 1949, 1950. Attention is directed to the fact that if the blood sugar value is over 120 mg. per 100 cc., 69 per cent were above 200. There can be no doubt that we are finding diabetics with such a campaign. It is not unlikely that of those cases in which the postprandial blood sugar values range from 120 to 199, one-half to two-thirds will eventually become diabetic.

TABLE 4 Diabetes Case Finding Campaigns in 1948, 1949, 1950

DATE	NEW CASES FOUND			
	GLYCOSURIA No. of Cases	BLOOD SUGAR Tests Made	BLOOD SUGAR ABOVE 120 Diabetes (almost certain)	BLOOD SUGAR OVER 120 Diabetes (probable)
1948	604	450	158	206
1949	197	143	48	66
1950	459	285	77	127
Totals	1260	878	283	399

Table 5 shows the age and sex distribution in the cases in which the postprandial blood sugar was over 120 mg. per 100 cc. Of the individuals, 72 per cent were about 50 years of age and about two-thirds of these were women.

TABLE 5 1950 DIABETES CASE FINDING CAMPAIGN. Cases in which the post prandial blood sugars was over 120 mg. per 100 cc. (excluding known diabetics).

AGE	MALE	PER CENT	FEMALE	PER CENT	TOTAL	PER CENT
1 to 29	0		1	1.0	1	1.0
30 to 49	10	13.0	10	13.0	20	26.0
50 and above	21	27.0	35	45	56	72.0
Totals		40.0		69.0		

COMMENTS

A question with which students of diabetes are greatly concerned is the number of undiagnosed diabetics. Surveys such as this one do not answer that question because, as we have shown, there is a shift in the age and sex of the survey population that is completely

out of line with the normal distribution of the population. It is important to realize that the survey population contains many individuals who are related to diabetics, as well as being obese. Such a group show a high incidence of glycosuria and hyperglycemia. In this campaign we found 1.75 per cent of the survey population had postprandial blood sugar of 120 or above, or one in every 57 persons. This incidence of unknown diabetes may be as much as double the normal incidence of the population.

The use of dried urine on a strip of filter paper and plastic such as we used, facilitates studies not possible when urine is collected in the fluid state. For instance, in our campaign, in the division concerned with employees, the workers were urged to take home enough strips for all members of the family. That this was done seems likely because the age and sex distribution of the group varied only a slight degree from that of the population surveyed through the drug stores. The employee group tended to be only slightly toward a younger age, the sex distribution did not vary from that of the general public. In the same manner school children, or any group of people, could be sent home with strips for the whole family.

The use of groups of people who are associated in some way has advantages over the attempt to survey the general public. This we feel is true, because the publicity needed can be more easily directed to such a group. It is simpler to obtain the cooperation from a related group of people than to get the needed newspaper and radio cooperation necessary in a campaign aimed at the public in general. On the other hand, if we are to succeed in a campaign of education of the public, the effort required to obtain newspaper and radio publicity is worthwhile.

In the development of the strip we had in mind the fact that in thousands of towns and cities there would be only a limited number of physicians interested in diabetes. Therefore we visualized a technic whereby one physician with the help of a small group of lay persons could conduct a campaign with a minimum of time and effort. If the post office department can be convinced that dried urine can be mailed with safety and without the use of expensive containers we can visualize reaching our vast rural populations.

There is a lesson emerging from this work that speaks for itself. Chronic disease demands early diagnosis. At the present time we do certain routine laboratory tests on all individuals entering the hospitals. The cost of a routine *postprandial* blood sugar would be very little and it seems strongly indicated in every patient; certainly those past 40 years of age, and those who are overweight. The custom of collecting the first voided specimen in the morning for routine laboratory examination undoubtedly results in missing mild diabetes, as does the routine of making blood sugar tests in the fasting state.

SUMMARY

The technic and results of a 1950 diabetes testing campaign in St. Louis, Mo., are described. A device for collecting dried urine samples on filter paper strips, called the St. Louis Dreypak, was used, making it possible for 1,000 specimens to be examined in one hour.

Of 5,087 strips collected from the general public (12 per cent of those distributed through 270 drug stores), 391 or 7.7 per cent gave positive tests for sugar. Of 1,923 strips collected from workers' families (14.8 per cent of those distributed through four industrial concerns) 68 or 3.5 per cent were positive.

Age and sex were found to be important factors in those actively participating in the tests. Mature adults and older people, especially women, predominated.

Those persons showing positive tests of glycosuria were invited to submit to a blood sugar test and 61 per cent accepted. Of 280 individuals who had glycosuria, 145 had postprandial blood sugar values less than 120 and 135 had blood sugar values ranging from 120 to 400. In the last group of 135, 72 per cent were about 50 years of age, and of these about two-thirds were women.

The convenience and rapidity of this method of collecting and examining urine for sugar is described. Its superior efficiency to other methods of large-scale urine testing is demonstrated.

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THE TEACHING OF SPECIFIC DYNAMIC ACTION

The phenomenon of specific dynamic action seems to be a source of misunderstanding and perplexity to a great many students and to many teachers of biochemistry and physiology. I would like to suggest that the reason is the way the subject is usually presented by lecturers and in textbooks.

The student is likely to be told that the ingestion of protein equivalent to 100 kcal gives rise to 130 kcal. He may be told that carbohydrate and fat also have a specific dynamic action, but in small degree. He will probably be told that, to allow for this, extra kilocalories must be added to the food intake that meets basal and activity requirements. An obvious way to think about these statements, is that, if kilocalories are required to release those of the food, their release in turn must depend upon the expenditure of other kilocalories. How, then, can the effect be overcome? How can there be caloric equilibrium, or positive balance, or growth, and why do we not waste away because we eat? . . .

The important thing in this particular case is that specific dynamic action has been demonstrated, and what it is and what it implies should be outlined. The following proposal provides a means of doing this without leading to perplexity. It depends upon stressing the relationship of specific dynamic action to the basal metabolism, which is more important than its relationship to the food.

When food is given to an animal under basal conditions, theer is a subsequent period when the metabolism rate is higher, even though the same conditions are maintained. The length of this period and the degree of elevation above the basal depend principally upon the kind and quantity of the food. For any one food or food mixture the total increment is proportionate to the amount fed. Foods high in protein have the greatest effect. It follows that under such conditions, if the caloric value of the food given does not exceed the basal expenditure plus the increment, there will be negative caloric balance.

Quantitatively, the specific dynamic action is the energyy increment to the basal which results from food utilization. The importance of the relationship of specific dynamic action to the basal metabolism must be realized for a proper understanding of the phenomenon. . . .

Suppose that an individual under basal conditions expends 60 kcal/hr. He is given food with a caloric value of 200, as a result of which during the next 5 hr. he expends not 300 but 320 kcal, at the end of which time the metabolic rate has returned to the basal level, and extra kilocalories equivalent to 10 per cent of those provided have been expended. The basal expenditure of this individual is 1440 kcal/day. If just the basal requirements are supplied by this particular food, therefore, there will be an expenditure of 10 per cent more, or 144 extra kcal; and even if the individual remains under the same conditions his total energy requirements will not be met. In this hypothetical case they will just be met, however, by 1600 kcal (1440 plus 10 per cent of the ingested), and there will be positive caloric balance with anything over 1600—e.g., a surplus of 45 calories from 1650, of 810 kcal from 2500, etc.—which could be used to support activity over the basal. Such a presentation should be suitable and adequate to explain what specific dynamic action is without leading to any misunderstanding.

At this stage, however, the student might be aided in evaluating specific dynamic action as a metabolic phenomenon by the following facts. Practically all our knowledge of specific dynamic action has been derived from studies of animals kept warm in the fasting state, and otherwise under basal conditions. Practically nothing is known about it in human beings under ordinary conditions of activity and everyday living, and under normal food consumption at the usual intervals. Ten per cent of the basal used to be regarded as the allowance to be made for specific dynamic action in human energy economy, but it probably should be smaller. The supposition that, because of its greater specific dynamic action, a high-protein diet is particularly beneficial in a cold environment has not received experimental support.

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Results of a Screening Program for Diabetes Mellitus

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BOSTON, MASSACHUSETTS

Studies of diabetes mellitus in recent years have indicated that the incidence of undiagnosed cases of this disease is nearly as great as the incidence of known cases under treatment. Blotner's[1] study of selectees during World War II disclosed the presence of diabetes in 1.1 per cent of 69,088 young men undergoing physical examination at the Induction Station in Boston, Massachusetts. In another study, the U.S. Public Health Service made a survey of the town of Oxford, Massachusetts,[2] in which 3516 persons were interviewed and tested. It was found that 40 were known diabetics. The screening tests brought to light 30 "new cases" of diabetes and 25 cases of unclassified glycosuria and hyperglycemia. In another survey carried out by the U.S. Public Health Service in Jacksonville, Florida,[3] 736 blood relatives of a group of known diabetics were tested, and 4.1 per cent of these persons were found to have unsuspected diabetes. These and other studies have alerted the medical profession and public health agencies to the magnitude of the challenge which is presented by the estimated "million unknown diabetics" in the United States. This challenge has been met in part by the Diabetes Detection Drives sponsored each year by the American Diabetes Association assisted by State and County Medical Societies and other interested agencies.[4]

The success of these Detection Drives has demonstrated a remarkable public interest in diabetes, and a desire on the part of the public to avail itself of the simple tests which can disclose the presence of the disease. One of the problems facing agencies interested in finding new cases of diabetes has been to get large groups of persons together so that screening tests for diabetes can be done quickly and economically. In this connection the experience of the Diabetes Fair in Boston may prove to be a valuable guide to future detection drives.

Each year since 1950, the New England Diabetes Association has sponsored a Diabetes Fair.[5] As part of this free educational program, all who came were offered tests of the urine and blood for glycosuria and hyperglycemia. The methods used and the results obtained in the mass testing of the 1951 Diabetes Fair are here described in detail.

Each person wishing to be tested was first required to register. A volunteer helper recorded on a numbered card the subject's name, age, sex, home address, and his answers to three questions: Are you a diabetic? Have any relatives had diabetes? Have you ever had sugar in your urine? In answer to the first question, the subject could reply, "Yes," "No," or "Doubtful." The other two questions required a reply in the affirm-

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ative or negative. A urine specimen was then obtained and immediately tested for sugar by trained technicians. Females were tested by the Galatest method and males by the Clinitest method.* The subjects were then invited to proceed to the blood-testing booth, where a staff of technicians drew capillary blood for analysis of the blood sugar by the Wilkerson-Heftmann method,[7] in the Hewson Clinitron.[8] It should be pointed out that this method is simply a screening test which provides a positive or negative result above or below any desired level of blood sugar, and does not give the actual blood sugar content. At the Diabetes Fair the test was set to give a "positive" result above the level of 160 mg. per 100 cc. The Clinitron† is a machine which enables a small staff to process as many as 120 blood samples in one hour. At the Diabetes Fair blood testing was carried out continuously from noon to 8:00 p.m. without regard to time elapsed since the subject's most recent meal.

After the blood was drawn, each person was asked to wait for a report on the test. As soon as this was obtained, the subject was called by number, and was interviewed by a physician who told him the results of both the urine and the blood tests and gave him a cautious interpretation of them. Whenever a positive test was found, either glycosuria or hyperglycemia, the subject was urged to consult his own physician, and the importance of this was particularly stressed when it was thought that the tests and the interview suggested the presence of diabetes.

RESULTS OF TESTS

In the two days of the 1951 Diabetes Fair, a total of 2280 urine samples were tested for the presence of sugar, and 888 blood samples were tested to determine whether the true blood sugar value was above or below 160. The results are shown in Table 1 to 4. The large number of known diabetics tested, and the still larger number of subjects with a history of glycosuria and/or a family history of diabetes could be anticipated from the character of the Fair, which naturally attracted, in particular, persons who had some interest in the disease. As shown in Table 1, there were 323 known diabetics. A considerable number expressed themselves as being "doubtful" as to whether they had diabetes. In the subsequent interview it was found that many of these were actually under treatment for diabetes, and that many others had preferred that answer to a simple "No" because, after all, they had never before been tested. In tabulating the results, as many as possible of these were re-classified, leaving as "doubtfuls" only 139 persons in whom a reasonable doubt appeared to exist. 113 of these had a history of glycosuria. The total number of "nondiabetics" with a history of glycosuria was 275,

TABLE 1 Results of questionnaire

	Males	Females	Totals
Number registered	821	1459	2280
Known diabetics	152	171	323
"Doubtfuls"	65	74	139
History of glycosuria (Known diabetics excluded)	111	164	275
Positive family history	239	515	754

TABLE 2 Results of blood and urine tests (known diabetics excluded)

	Males	Females	Totals
Number tested	669	1288	1959
Negative urine only	484	748	1332
Negative urine, negative blood	112	297	409
Positive urine only	8	20	28
Positive urine, negative blood	33	162	195
Negative urine, positive blood	9	12	21
Positive urine, positive blood	23	49	72

TABLE 3 Analysis of questionnaire and positive tests (known diabetics excluded)

	Number Tested	Positive Urine	Per cent	Positive Blood	Per cent
Negative questionnaire	1113	148	13.4	37	3.3
Positive family history only	543	63	11.2	16	2.9
"Doubtfuls"*	139	48	34.5	29	20.8
History of glycosuria only**	162	35	21.6	11	6.7
Total	1957	294	15.0	93	4.7

*Of the "doubtfuls" 113 had a history of glycosuria, and 59 had a family history of diabetes.
**57 of this group had a family history of diabetes.

TABLE 4 Results of tests in 323 known diabetics

	Urines Tested	Positive Urine Test	Per cent	Bloods Tested	Positive Blood Test	Per cent
Males	152	50	32%	84	32	37%
Females	171	86	50%	111	62	57%
Totals	323	136	42%	195	94	48%

TABLE 5 Analysis of replies to follow-up questionnaire

	Pos. Urine Pos. Blood	Neg. Urine Pos. Blood	Urine* Pos.	Total
Number of positive tests	72	21	223	316
Number of replies	64	17	174	255
Consulted a physician	54	13	112	179
Physician diagnosed diabetes	31	3	16	50
Physician denied presence of diabetes	9	8	80	97
Physician made no definite statement	11	2	13	26
Physician prescribed diet	44	5	48	97
Physician prescribed insulin	17	1	4	22
Subject had previously diagnosed diabetes	5	—	4	9

*10% of this group had the urine test only; 90% had also a "negative" blood sugar test.

* Reagents for these tests were supplied by the Denver Chemical Mfg. Co. and the Ames Company, Inc., respectively.

† The Clinitron was loaned by the U.S. Public Health Service.

and the number of "nondiabetics" with a family history of diabetes was 649.

Table 2 lists the results of the laboratory tests in the nondiabetics. 72 persons, or 3.6 per cent of the group had both glycosuria and hyperglycemia, and approximately half of these had definite symptoms of diabetes, 21 persons had hyperglcemia without glycosuria, 195 persons had glycosuria without hyperglycemia; but the marked disproportion of females to males in this group strongly suggests that many of the urine tests done on women (The Galatest was the method used) were erroneously called positive.

A further analysis of these figures (Table 3) attempts to correlate the laboratory data with the information given by the subjects. Here it appears that in the group of nondiabetics the incidence of glycosuria was 15 per cent and that of hyperglycemia was 4.7 per cent. That those persons with a history of glycosuria showed an incidence of positive urine and blood tests well above the average is perhaps not surprising. The very high percentage of positive tests among the "doubtfuls" suggests that this group harbored a considerable number of known diabetics who were merely reluctant to admit the fact, or who chose to doubt the accuracy of the previous diagnosis. It is thus impossible to estimate the actual number of "new cases" discovered. Further information obtained through a follow-up study suggests that the number of new cases was close to 100. It is realized, of course, that a lower blood sugar screening level—130 for example—would have disclosed a larger number of hyperglycemics, and that the opportunity to question these subjects in more detail, and to re-test them by more precise methods would have made possible many more accurate diagnoses. [8, 9] This task had to be left to the private physician. The purpose of the screening tests at the Diabetes Fair was primarily an educational one, to show that such tests are available, and can be of great diagnostic significance. The detection of new cases was only a secondary aim.

As shown in Table 4, 323 admitted diabetics were tested. It was interesting to find that 42 per cent of this group had glycosuria and 48 per cent of those who submitted to a blood test had hyperglycemia. This is perhaps not so surprising as the fact that the women diabetics showed a much higher incidence of hyperglycemia than did the men. The interviews with these subjects indicated that the majority were under active treatment. However, it was found that a considerable number had allowed treatment to lapse, and some had not consulted a physician for as long as 10 years.

DISCUSSION

The experience of the New England Diabetes Association in Boston indicates that mass testing of a large group of people attracted by an interest in diabetes can be expected to disclose a considerable number of new cases of the disease. A comparison of the results with those of the other surveys mentioned as references above suggests that a Diabetes Fair may be one of the best ways of finding new cases. The value of a Fair cannot, of course, be measured entirely by the number of newly discovered cases. The stimulation of interest in the disease, the educational features providing accurate information for the uninitiated and a "refresher course" for the diabetic, and the general good will created—all these have to be counted as being of even greater value, and without these features, it is unlikely that such a large group could have been reached.

FOLLOW-UP STUDY

The value of this method of diabetes detection could be checked further by ascertaining what action was taken by those persons whose tests were found to be abnormal. Did they seek medical advice, as they had been advised to do? If so, did the physician confirm the diagnosis of diabetes? And did he prescribe diet and insulin? The New England Diabetes Association undertook a follow-up study designed to settle these points.* Three months after the Diabetes Fair each of the 316 persons with positive tests was sent a questionnaire, and replies were returned by 255 persons in the next 2 months. The results, recorded in Table 5, show 179 persons, or 70 per cent of those replying had consulted a physician. The diagnosis of diabetes was confirmed in 50 cases. There were 97 cases in which the physician said that diabetes was not present. In 26 instances the replies indicated that the doctor had made no definite statement regarding the diagnosis. A diet was prescribed in 97 cases, or more than one-half of those who consulted a physician; 22 persons received treatment with insulin. The replies of 9 persons gave information which showed that the diagnosis of diabetes had been made prior to the Diabetes Fair.

In each of the 50 cases in which the diagnosis was confirmed, the patient was given a diet prescription; in 22 cases insulin was also advised. An additional 47 persons were given diet prescriptions by their physicians. The replies to the questionnaires indicated that many of these were treated for simple obesity; but since most of those whose physicians made no definite

diagnosis were, nevertheless, placed on a diet, it seemed that some physicians found it easier to treat diabetes than to diagnose it. And finally, there was a small group of persons who though they had failed to consult a physician had imposed on themselves diet restrictions which in most instances had resulted in freedom from glycosuria.

Table 5 has listed the subjects in 3 categories according to results of their laboratory tests. Those with both glycosuria and hyperglycemia showed the highest percentages of positive answers: That is, a larger proportion of this group consulted a physician, were diagnosed as diabetics, and were given diets and insulin. Several factors appeared to contribute to this. Many of these persons had come to the Fair because they suspected the presence of diabetes either on account of previous positive tests, or the presence of symptoms. The unequivocal nature of positive tests in both urine and blood, and the emphasis placed on this at the interview undoubtedly served to impress both the patient and the physician he subsequently consulted. In the group of 223 persons with glycosuria only (and most of these also had a blood sugar test reported as under 160) the percentage of positive answers to the questionnaire was smallest. Nevertheless, the family doctor made a diagnosis of diabetes in 16 of the 112 who sought medical care and prescribed a diet to 48 of these.

The questionnaire from which the above replies were tabulated allowed space for the subject to volunteer additional information if he so desired. Perhaps one-third of those who returned the form furnished an account of their subsequent medical experience which throws considerable light on the reaction of doctor and patient to the suspicion of diabetes. It was apparent that among the doctors consulted there was a wide range of skill, knowledge and interest shown in attacking the problem of diagnosis. Some physicians gave glucose tolerance test; others studied the post-prandial or the fasting blood sugar. Several doctors were content merely to test the urine for sugar, and finding it negative, had told the patient that he did not have diabetes. A few instances were reported where the doctor had made no tests at all.

There were 76 persons who answered the questionnaire even though they had not consulted a physician. Many of these furnished excuses for this neglect, particularly lack of money and doubt as to what doctor to consult. Several were still "planning to see a doctor" (five months after the Diabetes Fair); others were "too busy," or "took sick" or "afraid of the needle."

It is evident from these accounts that much remains to be done to render diabetics detection drives more effective. In particular, there is a need of more accurate knowledge of the criteria for the diagnosis of diabetes, and a greater appreciation on the part of the medical profession that early and continuous treatment of "mild" diabetes can prevent or delay many serious complications. Much of the resistance of the patient will disappear as the physician devotes more of his time and energy to the diagnosis and treatment of diabetes.

SUMMARY

The screening tests at the 1951 Diabetes Fair in Boston are described: 2280 persons were tested for glycosuria, and 888 persons were tested for hyperglycemia in the course of 2 days. Excluding 323 admitted diabetics there were 93 cases of hyperglycemia and 223 cases of glycosuria. It is estimated that approximately 100 "new cases" of diabetes were found.

A follow-up study of this group with abnormal screening tests showed that the physicians whom these subjects consulted made a diagnosis of diabetes in 50 cases, prescribed insulin for 22, and a diet for 97 persons.

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A DIABETES FAIR

Report on a Successful Educational Service

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A "Diabetes Fair" has been presented annually since 1950 by the New England Diabetes Association during Diabetes Week. [1-4] The purposes are to present authentic information concerning diabetes by means of exhibits and lectures and to demonstrate methods of testing urine and blood sugar in order to discover previously unknown cases of diabetes.

Widespread public interest has been created by these exhibitions. It was estimated that more than 5,000 persons visited the Fair in 1950. In 1951, 5,562 persons, aged 2 to 89 years attended the Fair, by actual count. Roughly, 50 per cent more women than men were present.

ACCOMODATIONS

Exhibits were displayed and blood tests made in a spacious room of Horticultural Hall, Boston, measuring 53 by 123 feet. Motion pictures and talks were presented continuously in an adjoining room, measuring 28 by 58 feet and seating approximately 250 people. The testing of urine was done in lounges with toilet facilities for both men and women. Evening programs were presented in a lecture hall with a seating capacity of 500 persons and a public address system broadcast these lectures to visitors in the adjoining main exhibition hall.

EXHIBITS

A variety of exhibits presented information about diabetes, its detection, various phases of the disorder, its management and control. These included displays on such subjects as dietetics, pharmaceuticals, summer camps, insurance for diabetics, as well as electrical self-quizzing devices with indication for true and false answers. Instructed individuals were assigned to each exhibit to explain the displays and to answer questions. The dietary exhibits merit special mention. The central display was developed around the six exchange lists for milk, fruit, vegetables, bread, meat and fat as prepared by the Diabetes Section of the U. S. Public Health Service in collaboration with the American Diabetes Association and the American Dietetic Association. Subsidary exhibits displayed different types of daily meal menus, salads, vegetables, fruits, varieties of foreign bread, sandwich fillings, deserts, and beverages.

MOTION PICTURES

Motion pictures and film strips on diabetes were shown continuously. There was much interest shown in the two motion pictures exhibited. The first, "They Live Again", was a 16mm. black and white sound film which ran approximately 11 minutes and told the story of the discovery of insulin by Doctors Banting and Best. It is available on loan through the Committee on Medical Motion Pictures of the American Medical Association. The second, "The Story of Wendy Hill", described the experiences of a young diabetic woman. This is a 16mm. color and sound film which runs for 20 minutes; it is available on loan from most State Health Departments. The film strips shown dealt with 11 subjects under such headings as "Eating for Good Health", "Planning Good Meals", "Insulin and its Use", "Diabetic Coma", and "Care of Your Feet". They, too, are available on loan from State Health Departments.

*Chairman, Committee on Public Education and Diabetes Detection, New England Diabetes Association. Other physicians who participated include: Doctors F. N. Allan, W. Finnerty, R. Harwood, A. A. Horner, D. Hurwitz, A. P. Joslin R. C. Larcom, A. Marble, L. T. McDaniel, J. Rosenthal, H. F. Root, R. P. Stetson, Hugh L. C. Wilkerson, P. White and others.

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TESTING

All visitors to the Diabetes Fairs were given the opportunity to have tests for diabetes made. Specimens of urine and blood were obtained and analyzed immediately so that the subject could watch the procedure. Most of the time there was a line of from 50 to 100 people waiting to be tested. Examination of the urine was made by the Galatest and Clinitest methods. Blood sugar determinations were made on capillary blood by the Wilkerson-Heftman method, [5] employing the Hewson Clinitron, an automatic machine for mass screening. After the results of these tests were obtained, the attending doctor gave the report to each individual. When glycosuria and hyperglycemia were found, the situation was discussed briefly. Stress was placed in advising a visit to the family physician to arrange for a final decision regarding diagnosis and treatment.

Each Fair has been presented without cost to the public; the expenses have been borne by the New England Diabetes Association, aided by contributions.

The assistance of many volunteers helped to make the Fairs successful. Technicians and physicians from the various Boston hospitals, members of women's auxiliaries of local medical societies, and many others gave valuable time and aid. Publicity was secured through newspapers, radio, medical journals and mass distribution of leaflets.

COMMENT

The Diabetes Fairs, conducted by the New England Association and endorsed by all state medical societies of New England, have served to present sound information to the public on the subject of diabetes and to promote good public relations between the medical profession and the population in the area. It is hoped that this and similar educational programs of the American Diabetes Association and its affiliates in other communities will contribute to the earlier detection and therefore the more effective treatment of diabetes.

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A view of Horticultural Hall, Boston during the 1950 New England Diabetes Fair, showing Testing Centers.

ABSTRACTS

ALEXANDER, GILBERT H.; AND LOWDER, RALPH J., JR. (*V.A. Hosp., Aspinwall, Pa., and Univ. of Pittsburgh Sch. of Med., Pittsburgh*): Definition of pancreatic cysts within pancreatic calcification: Report of two cases. Gastroenterology *21*:439-43, July 1952.

Two cases are presented in which cystic change within the calcified pancreas was predicted on the basis of the defect within the calcification. It is probable that detail study of pancreatic calcification will allow this feature to be recognized more frequently.

AMATUZIO, DONALD S.; SHRIFTER, NORMAN; STUTZMAN, FRANCIS L.; AND NESBITT, SAMUEL (*Vet. Admin. Hosp., and Univ. of Minnesota Med. Sch., Minneapolis*): Blood pyruvic acid response to intravenous glucose or insulin in the normal and in patients with liver disease and with diabetes mellitus. J. Clin. Investigation *31*:751-55, Aug. 1952.

No significant difference was found on comparing the fasting mean blood pyruvic acid of normal men and of patients with diabetes mellitus and compensated cirrhosis of the liver. After the administration of glucose, a statistically significant rise in the blood pyruvic acid occurred at 30 and 60 minutes in 17 normal men and 12 patients with compensated cirrhosis. An abnormal accumulation of blood pyruvate occurred with a normal glucose tolerance curve in three patients in liver coma. A delayed rise in the pyruvic acid of suggestive significance was found after glucose administration in 12 patients with mild diabetes mellitus requiring no insulin. A further significant delayed response of the blood pyruvic acid was found in 11 severe cases of diabetes mellitus. The degree of delay is apparently related to the degree of insulin deficiency of the pancreas and indirectly dependent upon the blood glucose level. A significant rise in the blood pyruvic acid was noted after the administration of crystalline insulin in 11 normal subjects. A similar response was noted in five patients with diabetes mellitus.

ALVAREZ, WALTER C. (*Chicago*): Carcinoma of the body and tail of the pancreas. Gastroenterology *21*:589-90, Aug. 1952.

The editorial reviews the high lights of the subject and gives some pertinent references.

ANNOTATIONS (*England*): Pre-diabetes. Brit. M. J. *2*:712, Sept. 27, 1952.

The existence of a prediabetic state is a relatively modern concept deriving much support from the observation of abnormalities in the obstetric records of women who ultimately develop diabetes. Many workers have reported the birth of large babies and a high rate of fetal loss in prediabetic women, and they have found a number of undiagnosed diabetics amongst women who have had large babies or stillbirths. There can be no doubt that some factor operates in the prediabetic woman to cause overgrowth of the fetus and a high rate of fetal loss for many years before clinical diabetes develops. A popular hypothesis claims that the overgrowth of the fetus and the subsequent maternal diabetes are both caused by an overproduction of somatropin by the maternal anterior pituitary. An obvious objection to this

hypothesis lies in the fact that acromegaly is very rare in the prediabetic woman. It seems that we must await the development of an efficient method for the assay of somatropin in body fluids before the validity of this hypothesis can be proved.

The theoretical importance of the concept of the prediabetic state is obvious, but it is small consolation to the diabetic woman to know that she has passed through this state. Nor is there much practical value in being able to predict the development of clinical diabetes in a patient if we can do little, apart from weight reduction, to prevent the inexorable advance of the disorder. However, should an effective method of prevention be discovered, the recognition of the prediabetic state would be of the greatest importance. At present, there are no means by which a definite diagnosis of prediabetes can be made. We know that certain circumstances, i.e., the birth of large babies and a high rate of fetal loss, are premonitions of a possible diabetic future. To these we may have to add hydramnios and toxemia of pregnancy, and if there is a family history of diabetes and the patient is obese, the premonitions become virtual promises. The minor changes in carbohydrate tolerance which some consider to be prediabetic tend to be inconstant in the individual and are of doubtful significance. Much more long-term study will be required before we can assess the risk of the development of diabetes in any one patient. At the same time it will be necessary to search for other signs which will increase the accuracy of our prognosis.

A recent observation that prediabetic fathers beget big babies is also of much interest and destroys the complacency with which we have hitherto blamed the mother alone for the overgrowth of her fetus, though apparently she is still responsible for the high rate of fetal loss. It is to be hoped that further studies of the prediabetic state in the father will soon be made.

ARTETA, J. L. (*Inst. of Exper. Endocrinol., Madrid*): The mechanism of the protective action of clamping the renal pedicles of dogs with alloxan diabetes. J. Endocrinol. *8*:245-49, July 1952.

When the renal pedicles of a dog are clamped, there is a reflex change in the circulation caused by excitation of the sensory nerve fibers of the vessels. The efferent reflex impulse passes along the splanchnic nerves. When these nerves are cut, the protective action of clamping of the renal vessels of dogs injected with alloxan disappears. The production of this vascular reflex, in the author's opinion, is a reason for the protection obtained through clamping of other vascular pedicles, viz., splenic (Houssay) or hepatic (Arteta), since the effect is not specific. The presence of the kidney is not absolutely necessary, and its lesions do not play an important role in the production of alloxan diabetes. Renal lesions, however, must be taken into account when they are severe, as when high doses of alloxan have been used, because they aggravate diabetes by adding the toxic effects of retention of urea to the diabetes. It is possible that excess of urea in tissue fluids and in cells facilitates the passage of toxic substances, thus reinforcing their action (Arteta and Domînguez, 1951).

BARNBROOK, D. H. (*Halifax, Nova Scotia*): Impermanent diabetes: A complication of traumatic pancreatitis. Canad. M. A. J. *67*:143-44, Aug. 1952.

In this case, diabetes of a transitory nature was initiated by a crushing injury.

BEASER, SAMUEL B. (*Beth Israel Hosp., Boston*): Medical progress: Diabetes mellitus. New England J. Med. *247*:353-59; 397-403, Sept. 4 and 11, 1952.

This comprehensive review covers the literature on diabetes mellitus during the past year. The review is divided into the following subdivisions: biochemistry and physiology, pathology and pathogenesis, experimental diabetes, diagnosis, treatment, associated conditions, surgery and diabetes, pregnancy in diabetes, and complications.

BELL, DAVID M.; AND BURNS, THOMAS (*Sch. of Med., Duke Univ., Durham, N. C.*): Effect on femoral A-V glucose difference of insulin injected into an antecubital vein and into a femoral artery. J. Clin. Investigation *31*:717-20, July 1952.

The injection of 1/80 unit of insulin per kilogram into an antecubital vein of human subjects caused a decrease in the femoral arteriovenous glucose difference. The injection of 1/80 unit of insulin per kilogram into the right femoral artery caused an increase in the arteriovenous glucose difference in the injected extremity and a decrease in the opposite extremity. The data indicate that the removal of glucose in the leg can be increased by the action of insulin; however, when insulin is given

intravenously in doses of 1/80 unit per kilogram, the lowering of the arterial sugar is caused by the action of insulin on other tissues more sensitive to it than the lower extermity.

BERNSTEIN, LIONEL M.; FOLEY, EDMUND F.; AND HOFFMAN, WILLIAM S. (*Hektoen Inst. for Med. Res., Cook County Hosp. and Depts. of Med. and Physiol., Univ. of Illinois Coll. of Med., Chicago*): Renal function during and after diabetic coma. J. Clin. Investigation 31:711-16, July 1952.

The specific clearance methods of Homer Smith were utilized for the study of renal function during and after diabetic coma. The six cases could be divided into two groups. In the four patients of Group 1, there was, at the time of coma, a reduction of C_M, C_{PAH}, and Tm_{PAH}. These were quickly restored to normal or supernormal values after repair of dehydration and electrolyte deficits. These rapidly reversed alterations of renal function were believed to be caused by dehydration, with its accompanying decrease in blood volume, cardiac output, and renal blood flow, and by the exaggeration of the last defect by the renal hemodynamic response to such dehydration. In contrast, the two patients in Group 2 showed azotemia, which progressed in spite of correction of water and electrolyte loss and which lasted two weeks. Several days after recovery from coma, C_M, C_{PAH}, and Tm_{PAH} were still markedly reduced and the ratios were distorted. Only slowly did these values return to normal. In these patients the renal ischemia had apparently produced a reversible organic lesion similar to that found in "lower nephron nephrosis," except that it was milder and was not accompanied by initial oliguria.

BHATTACHARYA, B. K.; BROACHA, S. B.; and DE' LIMA, TONY (*The Cipla Inst. for Therapeutic Res., Bombay 8, India*): The metabolic fate of invert sugar: Absorption, excretion and the effect of insulin on the utilization of sugar. Indian Journal of Medical Research 39:377-90, July 1951.

In insulin-induced experimental hypoglycemia in rabbits, intravenous injection of glucose raises the blood sugar a little above the normal within one hour, whereas injections of invert sugar and fructose raise the blood sugar to a level well below the normal.

BLEISCH, VIRGIL R.; MAYER, JEAN; AND DICKIE, MARGARET M. (*Harvard Sch. of Pub. Health, Boston, and Jackson Memorial Lab., Bar Harbor, Me.*): Familial diabetes mellitus in mice, associated with insulin resistance, obesity and hyperplasia of the islands of Langerhans. Am. J. Path. 3:369-80, May-June 1952.

A strain of obese mice with constantly associated diabetes and insulin resistance has been studied in comparison with clinically normal siblings and parents and with Swiss mice. The obesity is inherited as a simple Mendelian recessive. The obese mice exhibit larger, more numerous islands of Langerhans and other evidences of a stimulus to island growth. The siblings manifest slight evidence of a similar stimulus. Structural changes of other endocrine organs have not yet been demonstrated. The obese mice have less than normal amounts of hepatic glycogen. Cutaneous atrophy and ulcers which did not heal were found in some of the obese animals. The association of changes in the islands of Langerhans with insulin resistance and hyperglycemia suggests the existence of an insulin antagonistic factor which results in island growth primarily or secondarily. This may be an inherent metabolic antagonist. The low liver glycogen content in obese mice and the lability of blood sugar levels implicates the glycostatic theory of the regulation of appetite in the causation of the obesity, and possibly of the diabetes, in these experimental animals.

BOLLMAN, JESSE L.; AND GRINDLAY, JOHN H. (*Div. of Exper. Med., Mayo Found., Univ. of Minnesota, Rochester*): Measurement of renal gluconeogenesis. Am. J. Physiol. 170:38-44, July 1952.

In an investigation of the renal formation of glucose as a source of blood sugar, the authors found that differences in the glucose content of renal arterial blood and venous blood, simultaneously withdrawn from resting trained dogs were insignificant. No appreciable differences were obtained in fasting or fed animals or after injection of insulin or a single injection of glucose. Considerable differences in renal arterial and venous blood sugar were obtained in animals excreting glucose during continuous injection of glucose or following administration of phlorhizin. The amount of sugar found in the urine was less than that calculated as being removed from the blood during the same period. The amount of sugar which was removed from the blood and which did not appear in the urine varied considerably in different experiments. The amount of sugar

utilized by a kidney or the amount of sugar formed by a kidney of the resting dog is less than the margin of error inherent in the methods used for its detection.

BORNSTEIN, J. *(Dept. of Chemical Pathology, King's Coll. Hosp., London):* Further observations on the "anti-insulin" activity of diabetic plasma. J. Endocrinol. 7: October 1951 [From the Proceedings of the Society for Endocrinology, pages 59-60].

The injection of the plasma of some diabetic patients into alloxan-diabetic, hypophysectomized, adrenalectomized (ADHA) rats results in a diminution of sensitivity to insulin in these animals. Insulin could not be demonstrated in the plasma of these patients. Plasma containing a measurable amount of insulin, taken from the six obese middle-aged patients, failed to alter the sensitivity of the ADHA rats. Plasma containing no detectable insulin from three of the six patients also failed to affect the sensitivity of these rats to insulin. However, plasma from the other three patients diminished the sensitivity of the preparations considerably. It is considered that in the first three patients of the group, the absence of insulin in the plasma is probably due to failure to secrete it; but in the other three, another factor leading to the lack of functional insulin is operating.

BRAY, P. T.; ISAAC, R. J.; AND WATKINS, A. G. *(Dept. of Child Health, Welsh Nat. Sch. of Med., Cardiff)*: Galactosaemia. Arch. Dis. Childhood 27:341-47, Aug. 1952.

Two cases of galactosemia in infants and a third case of probable galactosemia in a 7-year-old girl with cataracts, liver enlargement, and galactose intolerance are presented. The importance of early diagnosis is emphasized by the improvement shown in one case when the infant was placed on a lactose-free diet. It is suggested that the disease be called "galactosis."

BROWN, ADDISON W.; AND MARK, MILTON S. *(Des Moines, Iowa)*: Diabetes and pregnancy. J. Iowa M. Soc. 42:532-33, Nov. 1952.

The coexistence of pregnancy and diabetes is more commonly encountered today than in previous years. Many serious complications may occur but in the authors' experience, the obstetric course of the diabetic patient and fetal salvage closely approximated the course of the nondiabetic patient. They describe four important factors. 1. Careful control of the diabetes. 2. Adequate prenatal supervision to exclude preventable complications. 3. Termination of pregnancy at the 35th, 36th, or 37th week. 4. Termination of pregnancy by induced labor or by cesarean section, depending upon the individual case.

BROWN, E. M., JR.; DOHAN, F. C.; FREEDMAN, L. R.; DE MOOR, P.; AND LUKENS, F. D. W. *(George S. Cox Med. Res. Inst., Univ. of Pennsylvania, Philadelphia)*: The effects of prolonged infusion of the dog's pancreas with glucose. Endocrinology 50:644-56, June 1952.

Continuous infusion of 5 to 17 per cent glucose into the arterial circulation of part of the pancreas of normal dogs was carried out for periods as long as 18 days. Peripheral venous hypoglycemia occurred for variable portions of the total infusion period. Peripheral hyperglycemia was not observed. Some of the experiments provided striking evidence of the power of glucose to stimulate the secretion of insulin as judged by the resulting hypoglycemia. Infusion of the portal vein with similar amounts of glucose did not alter the blood glucose. Local hyperplasia of the islands of Langerhans was observed. In other areas, degranulation and early glycogen infiltration (hydropic degeneration) were seen. Both types of local change developed when the blood insulin was elevated, as indicated by the peripheral hypoglycemia. This differs from previous observations that insulin inhibits the growth of the islands and prevents or restores glycogen infiltration of the beta cells. Taken in conjunction with previous work, the findings indicate that insulin, the level of blood sugar, and no doubt other factors influence the activity of the islands of Langerhans. The present results emphasize the need for considering the balance or equilibrium of such influences under various experimental conditions.

COHEN, E. M. *(Pharmacological Lab., Univ. of Leiden)*: Polyuria and sugar excretion in alloxan diabetic rats. Acta physiologica et pharmacologica neerlandica 2:349-79, May 1952.

In alloxan-diabetic albino rats the volume of urine and the concentration of glucose rise with the blood sugar level until the latter attains a value of approxi-

mately 300 mg. per 100 ml. Above this value the urine volume continues its increase, but the percentage of glucose in the urine remains practically constant. The presence of a ceiling to the urinary sugar concentration cannot serve as an explanation, for by water deprivation the alloxan-diabetic rats could be made to excrete urine with the concentration of sugar exceeding 8 per cent. In accordance with the facts given in literature, the computed reabsorption of glucose by the kidney increases with the blood sugar level until a level of about 300 mg. per 100 ml. is attained. The fact that it diminishes again when the blood sugar level increases further led the author to to think that a possible explanation for the facts might be found by assuming an excretion of sugar, associated with an excretion of water, at blood sugar levels in excess of 300 mg. per 100 ml. The existence of such a mechanism, although thought to be highly improbable by the author, was not excluded by the results of preliminary experiments with carinamide.

COHN, CLARENCE; KATZ, BERTRAM; HUDDLESTUN, BERNICE; KOLINSKY, MURIEL; AND LEVINE, RACHMIEL (*Dept. of Biochem. and Dept. of Metab. and Endocrine Res., Med. Res. Insti., Michael Reese Hosp., Chicago*): Utilization of carbohydrate by extrahepatic tissues of the adrenalectomized dog. Am. J. Physiol. *170*:87-93, July 1952.

The authors report that the extrahepatic tissues of the adrenalectomized dog maintained with desoxycorticosterone utilize less carbohydrate than those of the normal animal. The amounts of glucose required by constant intravenous injection to maintain blood glucose levels in normal and in adrenalectomized, eviscerated, liverless animals are similar. These observations lead to the conclusion that the main metabolic action of adrenal cortical steroids is to promote gluconeogenesis by the liver from protein and probably from fat.

CREETH, J. M. (*Courtauld Inst. of Biochemistry, Middlesex Hosp., London*): Maximum molecular weight of insulin. Nature, London *170*:210, Aug. 2, 1952.

Current investigations on the molecular weights of enzymic digests of insulin prompted the redetermination of the sedimentation and diffusion constants of the untreated crystalline protein. The value of 35,000-36,000 refers to the maximum molecular weight of insulin as its exists in solution (investigations at *p*H 7.0 and 7.2 gave similar results) and therefore is in satisfactory agreement with the x-ray determination of the molecular weight in the solid state, namely, 36,000.

DANOWSKI, T. S.; HUFF, SUZANNE; ERHARD, LORAINE H.; PRICE, MARJORIE; BROWN, MINA; WIRTH, PATRICIA; AND STEVENSON, S. S. (*Children's Hosp. and Renziehausen Foundation, Univ. of Pittsburgh Sch. of Med.*): Protein-bound iodine levels in normal and in diabetic children. Am. J. Dis. Child. *84*:5-10, July 1952.

Serum concentration of protein-bound iodine was found to be statistically indistinguishable in diabetic children under treatment and in nondiabetic normal children.

DESPOPOULOS, AGAMEMNON; AND KAUFMAN, EDWIN H. (*Hosp. of Rockefeller Inst. for Med. Res., New York City*): Effect of desoxycorticosterone glucoside on renal tubular reabsorption of glucose in dogs. Am. J. Physiol. *170*:11-16, July 1952.

The intravenous administration of desoxycorticosterone glucoside (DCG) to either anesthetized or unanesthetized dogs resulted in a reversible depression of the renal reabsorptive capacity for glucose (Tm$_G$). The degree and duration varied with the dose. There was no consistent effect on the glomerular filtration rate. Desoxycorticosterone in equivalent dosages failed to produce similar alterations in tubular function.

DOWD, GEORGE C. (*Worcester, Mass.*): Senile diabetes mellitus: A cholinuric classification and approach to treatment. M. Times, New York *80*:537-39, Sept. 1952.

A study of fifteen cases of diabetes with neuropathy in elderly persons is presented. A classification, based upon choline excretion and hepatopathology, is discussed. A possible new approach to treatment is outlined.

DOWNIE, EWEN (*Melbourne*): The management of diabetes mellitus in general practice. M. J. Australia *1*:860-62, June 21, 1952.

Unlike most of the chronic or incurable diseases which are encountered in practice, diabetes mellitus, if properly controlled, should not prevent a patient from living a full and useful life. Also, unlike most of the diseases for which medical advice is sought, it is necessary for the patient to know something about his complaint and to appreciate the reasons which underlie his treatment. The function of the practitioner is twofold: first, to institute such measures as are appropriate to control the

hyperglycemia, and, second, to educate and encourage the patient in the way to keep it controlled. The accomplishment of these objectives is rewarded by the satisfaction of seeing the diabetic patient enjoying a normal life.

DUNLAP, ROBERT W., JR.; HALLENBACK, GEORGE A.; AND HANLON, DAVID G. (*Mayo Foundation for Med. Educ. and Res., Rochester, Minn.*): Portal hypertension associated with sarcoidosis and with hemochromatosis: Report of 2 cases with splenectomy and splenorenal anastomosis. Proc. Staff Meet., Mayo Clinic *27*:266-72, July 2, 1952.

A case of hemochromatosis with portal hypertension that was treated successfully by splenectomy and splenorenal anastomosis is reported. Diabetes was not apparent until eight months after the operation.

EDITORIAL (*Chicago*): Anticipation in inheritance of diabetes. J.A.M.A. *150*:796-98, Oct. 25, 1952.

Anticipation, or antedating, is a term applied to the phenomenon of the onset of a hereditary disease at a progressively earlier age in successive generations of an affected family. Harris, in his study of 1,241 diabetic propositi, felt that there was little or no parent-child correlation with respect to age in onset of the disease. Steinberg and Wilder feel that, because anticipation in diabetes is a statistical and not a physiological phenomenon, it would be desirable to discontinue the use of the term "anticipation" in referring to cases of prior onset of the disease in children of affected parents. The more noncommittal and more descriptive expression "prior onset," they feel, is to be preferred.

The prior onset of diabetes in the diabetic child of diabetic parents is observed frequently because the age of onset of diabetes is highly variable and includes the reproductive period, and nearly all diabetic patients who become parents become diabetic after the age of 30 years. There is no biological relationship between the age of onset in the parent and in the child. The age of onset of diabetes in a parent cannot be used to predict the age of onset in the children.

EDITORIAL (*San Francisco*): Diabetes—The ADA. Search *2*:256, October 1952.

Diabetes is most adaptable to control programs. Eighty-four-year-old Charles Cowan, of Anaheim, is the best living example of the potential control of diabetes. He was the first person in the United States to receive insulin and the first to change to a special carbohydrate diet. For thirty years he has been living a productive life. Prevention on a mass scale is progressing slowly in conjunction with other screening programs.

EDITORIAL (*Chicago*): Metabolism of fructose in the diabetic. J.A.M.A. *149*:1142, July 19, 1952.

The administration of glucose to dogs or normal human subjects leads to an increase in the pyruvate concentration and a decrease in the level of inorganic phosphate in the blood. These changes also occur when a diabetic patient receiving insulin is given glucose. The increase in the blood pyruvate, coupled with a decrease in inorganic phosphate content, has been used as an index of the metabolism of administered sugar.

The changes in the blood concentration of fructose, pyruvate, and inorganic phosphate following an intravenous injection of fructose indicates that the metabolism of fructose is different from that of glucose in both normal subjects and diabetics without insulin. The diabetic without insulin can metabolize fructose given intravenously in a manner similar to that of a normal person.

Since fructose normally enters the scheme of glycolysis subsequent to the point at which glucose is phosphorylated, the metabolism of fructose is consistent with the concept that the phosphorylation of glucose to glucose-6-phosphate is impaired in the diabetic. The phosphorylation of fructose, on the other hand, appears to proceed at its normal rate in the diabetic without insulin.

EDITORIAL (*New England Health Inst., Univ. of Connecticut, June 18-20, 1952*): Nutrition. Connecticut Health Bull. *66*:232, Aug. 1952.

Obesity is both a public and a personal health problem because of its apparent connection with specific diseases and with a shortened span of life. Most important in this relation are heart disease and diabetes. Deaths among men with diabetes and obesity are as high as 3.75 times those among diabetic men of normal weight. Experts in the field believe that the most important

cause of diabetes is obesity. One of the newer efforts being made to remedy the situation is group therapy.

FARRANT, J. L.; AND MERCER, E. H. (*Chemical Physics Section, Div. of Industrial Chemistry, Commonwealth Sci. and Ind. Res. Org., Melbourne, Australia*): Electron microscopical observations of fibrous insulin. Biochimica et biophysica acta *8*:355-59, April 1952.

When insulin is heated with dilute acids, it is converted into an insoluble form. Waugh has concluded that the insulin is converted into fine fibrils (F-insulin) which subsequently clump, leading to the visible precipitate. Electron micrographs of the fibrils of F-insulin show that these consist of fine fibrils of minimum width (50-80Å) and indefinite length. No periodic structure was found in the fibrils, but the tendency to split transversely is in agreement with the view that they are formed by linear aggregation of particles. The particle, which participates in the actual linear aggregation leading to fibril formation, seems to be larger than the 12,000 M.W. insulin molecule present in acid solution, and this suggests that a preliminary association of several molecules occurs before the actual linear polymerization.

FEINBLATT, THEODORE M.; AND FERGUSON, EDGAR A., JR., (*Brooklyn, N. Y.*): Variability of insulin response in standard rabbits. Southwestern Med. *33*:333, Sept. 1952.

The insulin response of rabbits follows a normal bell-shaped distribution curve. This curve holds true for the individual variation of all measurable animal traits except in cases in which at some point the variation is lethal.

FOREIGN LETTERS *(Paris):* Sodium citrate in vascular disease. J.A.M.A. *150*:152, September 13, 1952.

Intravenous injections of sodium citrate in doses not exceeding 0.15 gm. per kg. of body weight and given slowly as a 10 per cent solution have been reported by Courbin, and by Camelin and others to be effective in cerebrovascular complications. This treatment is especially indicated for plethoric hypertensive patients with hypercholesterolemia, azotemia, frequent precordial pain, visual disorders, and vertigo. Recent retinal changes improve. Ten seconds after the injection the patient experiences a peculiar feeling of freshness or a salty taste. Hypertensive diabetic patients are also relieved. Cerebral vascular spasms are rapidly influence with one injection every third hour. Arteritis and diabetic arteritis are also amenable to this therapy. Nothing certain is known in regard to the mode of action of sodium citrate, and only hypotheses are possible; there may be inactivation of the calcium ion by the sodium ion or a reduction of the viscosity of the circulating blood, the cause of many visceral disorders. The authors are also keeping in mind another possible explanation, the importance of the sodium ion in the cellular and blood electrolytic balance. A modification of the plasma tonicity, brought about by sodium citrate, may also occur. The experiments made by Professors Lein Binet, J. Vernes, and others show that citrate may be effective against arterial atheroma provoked by vitamin D_2.

FOREIGN LETTERS (*Argentina*): Insulin plant in Argentina. J.A.M.A. *149*:885, June 28, 1952.

After the war it was difficult to obtain pancreas and industrial equipment for the production of insulin, and there has been an insufficient quantity produced to fulfill the needs of Argentina. The frozen pancreas was sent to the United States and Europe. The Ministry of Public Health of Argentina has announced that the Armour Laboratories, of Chicago, are building an important plant for the production of insulin. The plan is to produce insulin for the 70,000 or more estimated diabetes victims of Argentina and to export 70 per cent of the production.

FORTUIN, FLOYD; AND WASSING, HANS (*Paterson, N. J.*): Diabetic neuropathy. J.M. Soc. New Jersey *49*:347-53, Aug. 1952.

Diabetic neuropathy usually develops in cases of non-regulated diabetes. Although in a homogeneous group of diabetics, the patients with neuritic involvement have, on an average, higher blood sugar levels than those without neuropathy; the hyperglycemia per se will not cause "nerve lesions." Whereas regulation of the diabetes seems, to date, to be the most important curative factor in diabetic neuropathy, it is not the establishment of a normal blood sugar per se that is the curative principle.

In the main, vitamin therapy has been of no help. Collens et al. produced some impressive graphs of improvement with massive doses of vitamins, with objective relief obtained in 60 per cent and subjective relief in 72 per cent. Psychological factors are of prime importance, particularly with respect to dietary irregularities, which are often protests against the physician's handling of his case or against the interference of parental (familial) figures.

FRANCISCO, ROBERTO (*San Juan Diagnostic Clin., San Juan, Puerto Rico*): The possible functional relationship of the "alpha" cells of the islets of Langerhans with an abnormal fat (cholesterol) metabolism. Preliminary report. Boletin de la Asociasión médica de Puerto Rico *44*:193-97, May 1952.

The theory is suggested that the alpha cells have a secretory functional relationship with fat (cholesterol) metabolism. Dysfunction or lack of function of these cells probably leads to an abnormal fat (cholesterol) metabolism as reflected in diseased states characterized by hypercholesterolemia, such as xanthomatosis, diabetes, hypothyroidism, coronary thrombosis, etc. The author postulates that a de-insulinized beef pancreatic extract, used successfully in a case with xanthomatosis and complicating objective and subjective evidence of coronary atheromatosis, is the alpha cell substance.

GLAFKIDES, CONSTANTINE M.; BENNETT, LESLIE L.; AND GEORGE, ROBERT (*Div. of Physi. and Inst. of Experimental Biology, Univ. of California, Berkeley*): Inhibition of the diabetes enhancing effect of ACTH by a diet high in potassium chloride. Endocrinology 50:684-86, June 1952.

It had been shown that a diet high in potassium chloride will inhibit the increase in urinary nitrogen produced by ACTH in normal rats. A study was made of the effects of such a diet on glycosuria produced by ACTH in diabetic rats. It was concluded that a diet high in KCl, when fed to diabetic rats with minimal or moderate glycosuria, inhibits the increase in glycosuria produced by minimum effective doses of ACTH.

GODLOWSKI, Z. Z.; AND PATERSON, H. (*Dept. of Path., Edinburgh Univ., and Ballochmyle Hosp., Edinburgh*): Rheumatoid arthritis of menopausal women treated with insulin hypoglycemias. Ann. Rheumat. Dis. *11*:36-38, March 1952.

In 10 cases, insulin hypoglycemia was induced by giving the fasting patient a subcutaneous injection of insulin at 8 a.m.; this was repeated daily for from 14 to 28 days. Nine of the 10 women showed significant improvement during and for some time after treatment; however, all relapsed during the succeeding 10 months, and in some the disorder progressed more rapidly than before treatment. Insulin hypoglycemia only temporarily retards the course of this type of rheumatoid arthritis.

GOFMAN, JOHN W. (*Univ. of California, Berkeley*): Diet and lipotrophic agents in atherosclerosis. Bull. New York Acad. Med. *28*:279-93, May 1952.

Two major features of atheroma formation are striking: (a) the focal characteristic of the lesion and (b) the abnormality in serum lipids associated with the development of the disease. The most plausible concept of its pathogenesis is that certain circulatory lipids are deposited and retained in susceptible focal areas to produce atherosclerotic lesions. The various histopathologic features characterizing the lesions may then represent the result of secondary processes, including possibly regressive changes, in the evolution of the mature disease.

Certain of the lipoproteins S_f 12-100 found in human serum are associated with atherosclerosis. Dietary measures, including caloric restriction and fat restriction, are capable of reducing the S_f 12-100 lipoprotein levels in a part of the human population. Neither measure is universally effective in reducing the lipoprotein levels; however, the response to one or another of the measures is of sufficient degree and frequency to warrant the trial of a low-fat diet plus correction of obesity as an approach to the reduction of S_f 12-100 lipoproteins in the management of atherosclerosis.

GOODMAN, JOSEPH R.; AND KANTER, SAUL (*Dept. of Investigative Med., Vet. Admin. Hosp., Long Beach, Cal.*): Cholesterol changes in schizophrenic patients during insulin therapy. A.M.A. Arch. Neurol. & Psychiat. *68*:534-38, October 1952.

A definite pattern of changes in the blood cholesterol level has been observed in schizophrenic patients during a course of insulin coma therapy. There was a definite and consistent increase on week ends after a five day series of treatments; this was followed by a decrease during the treatment periods. This pattern may pos-

sibly be related to the endocrine response of the patient to the therapy.

GREENHOUSE, BARNETT (*New Haven, Conn.*): The diabetic menu. Connecticut M. J. *16*:736-38, October 1952.

A typical menu includes for breakfast: orange juice, cereal and milk, toast, egg and coffee; for lunch: a sandwich, fruit, and coffee; for supper: a "blue plate" of meat, salad, a cooked vegetable, and potato plus a slice of bread, fruit, and tea; on retiring: milk and crackers. A pint of milk is allowed for the day.

With the use of insulin and within the limits of the patient's weight and needs, it is not necessary to restrict but rather to circumscribe the diet. The aim should be to see how much food a patient may have rather than how little. Although an overweight diabetic will need to reduce his food portions, a normal or underweight individual may enjoy bountiful servings. It is essential, however, that the diet be kept constant at whatever level it is adjusted in order to balance the insulin requirement against it, for it is easier to vary the insulin than to make diet changes.

GRUBER, M. (*Lab. of Physiol. Chem., Univ. of Utrecht*): Synthesis of fat from carbohydrate in thiamine deficiency. Acta physiologica et pharmacologica neerlandica 2:411-31, May 1952.

When a carbohydrate-rich diet sufficient for weight maintenance of full-grown pigeons was administered by forced feeding to pigeons on thiamin-deficient diets, a weight loss occurred. Determinations of the amounts of food not absorbed from the intestine and observation of the animals showed that this weight loss was chiefly due to a decrease of the amount of food absorbed from the intestine as a result of frequent vomiting of the thiamine-deficient birds. Thiamine deficiency leads to a partial blocking of some of the alternative pathways in carbohydrate metabolism without measurably influencing the total energy production from carbohydrate.

HALLETT, E. B.; HOLTON, G. W.; PATERSON, J. C. S.; AND SCHILLING, J. A. (*Depts. of Surg. and Path. Univ. of Rochester Sch. of Med. and Dent., Rochester, N. Y.*): Liver blood flow, hepatic glucose production, and splanchnic oxygen consumption in normal dogs and following Eck fistula. Liver blood flow before and after splenectomy. Surg., Gynec. & Obst. 95:401-406, October 1952.

The purpose of this study was to estimate the liver blood flow, hepatic glucose production, and splanchnic oxygen consumption in normal dogs and following Eck's fistula. The bromsulfalein test showed that there was a 50 per cent reduction of blood flow following Eck's fistulas, glucose production was unaltered, and splanchnic oxygen consumption was reduced approximately one-half, indicating that in the fasting state the liver is responsible for one-half the total splanchnic oxygen consumption. The effect of splenectomy on liver blood flow was unpredictable under these experimental conditions.

HARDY, JAMES D.; AND DRABKIN, DAVID L. (*Dept. of Surg., Univ. of Tennessee Coll. of Med.; Dept. of Physiological Chem., Grad. Sch. of Med., Univ. of Pennsylvania, and the Harrison Dept. of Surg. Res., Univ. of Pennsylvania*): Measurement of body water. Techniques and practical implications. J.A.M.A. *149*:1113-16, July 19, 1952.

The author discusses the overwhelming importance of water in the body economy. Water furnishes the preponderant single molecular element in the fabrication of tissue. Its presence is essential to the mass of chemical reactions on which life depends. It furnishes the means of transportation of virtually all enzymes, substrates, metabolites, gases, electrolytes, antibodies, and other substances that must be moved to and from the cell. Cellular function itself is affected by abnormal fluctuations in water content.

Body water and body fat bear a reciprocal relationship; that is, the less the fat content, the greater is the percentage of water contained in the body.

On a theoretical basis, body water and body fat must bear an inverse relationship to each other. To test this concept, the authors selected a group of healthy adult male and female human subjects ranging in size from the very lean to the very obese. Heavy water was injected intravenously and, after equilibration with the body water, the concentration of deuterium oxide in the water distilled from plasma samples was measured. The leanest male subject had a total body water value of 71 per cent of body weight (44.5 liters), and the most obese male subject had a total body water value of 42 per cent (48.3 liters). Similarly, the leanest female

subject had a total body water value of 68 per cent, and the most obese female subject a body water value of 50 per cent. These findings show an average of 60 per cent in males and 55 per cent in females. The commonly used value of 70 per cent is acceptable only in the unusually lean subject.

HART, JAMES C. (*Hartford, Conn.*): The preventive disease program in Connecticut: Diabetes. Connecticut Health Bull. *66*:259, September 1952.

At present, most of our attempts to control diabetes depend upon early detection and follow the recommendations of the American Diabetes Association. The diabetes detection program has been successfully carried out in Connecticut through the co-operation of physicians, druggists, hospitals, and public health workers. Attempts are being made to standardize the dietary treatment of diabetics by the use of the meal plans which have been set up by the American Diabetes Association in co-operation with the American Dietetic Association and the Diabetes Section of the U.S. Public Health Service.

HENDRY, W. GARDEN (*Highlands Hosp., Winchmore Hill, London*): Radical duodenopancreatectomy for papilloma of the pancreatic duct. Brit. M. J., 2:815-16, October 11, 1952.

A case of obstructive pancreatitis due to papilloma of the duct of Wirsung is reported. Its pathology, treatment, and postoperative course are detailed. The altered physiology is discussed.

HILL, ROBERT G.; ISON, E. C.; JONES, W. W.; AND ARCHDEACON, J. W. (*Dept. of Anat. and Physiol. Univ. of Kentucky, Lexington*): The small intestine as a factor in regulation of eating. Am. J. Physiol. *170*:201-05, July 1952.

Solutions containing a sufficient quantity of glucose in hypertonic concentration, when placed in the intestine of the dog by fistula, were effective in limiting food intake. Experiments with a non-nutritive fiber lend weight to the postulate that fullness, distention, or muscular activity of the intestine or a combination of these does initiate reflexes which at least temporarily dull the desire to eat. However, whatever degree of inhibition may be exerted does not seem to be of great magnitude. Tyrosine was not effective in inhibiting intake, as measured in these experiments.

HUGHES, R. F.; SWENSON, M. J.; UNDERBJERG, G. K. L.; AND HUGHES, J. S. *(Dept. of Physiol. and Chem. Kansas State Coll. Manhattan):* The function of vitamin C in in the adrenal cortex. Science *116*:252-53, September 5, 1952.

In a study of female guinea pigs on a vitamin-C-deficient ration, the authors observed that cortisone and vitamin C inhibited the development of arthritic lesions, whereas administration of ACTH and desoxycorticosterone resulted in severe arthritic lesions. These results are in accord with the theory that vitamin C is essential in the production of the oxy type of adrenal cortical hormones.

HURWITZ, DAVID; AND HIGANO, NORIO *(Harvard Med. Sch. Boston Lying-in Hosp. Boston):* Diabetes and pregnancy. New England J. Med. *247*:305-09, August 28, 1952.

Experience over an eighteen-year period with 140 diabetic pregnant patients is discussed from the standpoint of diagnosis and management during pregnancy. The incidence of fetal mortality could not be closely correlated with the severity or duration of maternal diabetes, except for a lower incidence found in mild diabates or in diabetes discovered during pregnancy. The incidence of toxemia (29 per cent) was increased as compared with that in nondiabetic women (7 or 8 per cent). A slightly higher incidence of toxemia was noted in cases in which intra-uterine or neonatal deaths occurred. The net mortality was 23 per cent, 72 per cent of which occurred before the thirty-seventh week. Whether or not earlier delivery than previously advocated will result in more live babies or more neonatal deaths from prematurity cannot be answered at present. Preliminary studies on a small group of patients treated orally with diethylstilbestrol appear to show a decreased incidence of fetal mortality and maternal toxemia. An ideal method of study is outlined for evaluating hormonal therapy.

JACKSON, W. P. U. *(Dept. of Med., Univ. of Cape Town, Cape Town, South Africa):* Studies in pre-diabetes. Brit. M. J. 2:690-96, September 27, 1952.

Using the 50 gr. single-dose glucose tolerance test and the Hagedorn-Jensen method for blood sugar determination in capillary blood, the author and his co-workers have defined a normal blood sugar curve at the 36th week and on the 6th post partum day as follows: below 120 fasting, below 200 at the maximum level, below 140 at the two-hour level, and below 130 at the two-and-a-half hour level. Two-hour levels between 120 and 140 mg. are slightly suspicious but probably normal. Two-hour and two-and-a-half-hour levels above these limits, with the rest of the curve normal, are often regarded as expected findings in pregnancy, but the author believes they are a warning of a prediabetic state. Two-hour levels over 140 mg. with a high fasting level and a high maximum level, or diabetic symptoms, must be regarded as frankly diabetic. Patients suspected of being diabetic may be expected to yield reliable information by being tested on the sixth day after delivery.

JOHN, HENRY J. *(Cleveland):* Up to four decades of hyperglycemia in diabetics without loss of carbohydrate tolerance. Metabolism *1*:400-12, September 1952.

Records are presented of seven patients of diabetes mellitus varying in duration from 14 to 37 years. Most of the time they had considerable hyperglycemia as evidenced by elevated levels of the blood sugar throughout the day in preprandial estimations. In these seven patients with hyperglycemia over periods of many years, the insulin could be reduced toward the end in three; in two the insulin requirement remained stationary; and in the other two there was a slight increase.

JOINER, C. L. *(Dept. of Med., Guy's Hosp. London):* Blood glutathione levels and carbohydrate tolerance during ACTH therapy. Brit. M. J. 2:642-43, September 20, 1952.

A study of the blood glutathione in a number of patients receiving ACTH therapy intravenously suggested that the decreased carbohydrate tolerance induced by the ACTH is not regularly accompanied by a detectable fall in the blood glutathione level. These results do not support the view that an alloxan-like action initiates the development of diabetic states.

KHEDROO, LAWRENCE G.; AND DI GILIO, MICHAEL M. *(Chicago):* Transient hyperglycemia and glycosuria associated with the acute abdomen. Illinois M. J. *102*:210-13, September 1952.

Two cases are reported in which transient hyperglycemia and glycosuria were considered to be the result of a normal body response to pathologic stress in an acute abdominal emergency.

KLOTZBUCHER, E. *(Leipzig):* Rectal insulin absorption with aid of hyaluronidase. Deutsche Zeitschrift für Verdauungs—und Stoffwechselkrankheiten einschliesslich Theorie und Praxis der Krankenernährung *12*:1-48, 1952 [*Abstr. from* J.A.M.A. *149*:1068, July 12, 1952].

The effect of rectally administered insulin was compared with that of subcutaneously administered insulin in persons without diabetes. The dose of insulin in each case was 10 units. It was found that when the rectal administration of insulin was preceded by introduction of hyaluronidase into the rectum, there was a reduction in blood sugar that amounted to 59 per cent of that induced by subcutaneous administration of insulin. Rectal administration of insulin without the preparatory hyaluronidase introduction caused a slight increase in blood sugar content, probably owing to an admixture of glycogenic substance.

KOCH, SUMNER L.: Laboratory aids in surgical diagnosis. Surg., Gynec. & Obst. *95*:243, August 1952.

In a study by Belk and Sunderman, 597 blood specimens of known composition were submitted to 59 hospitals and private laboratories. When the results were analyzed, 323, or 54 per cent, of the results obtained were unsatisfactory, with errors ranging from 89 per cent too low to 941 per cent too high. Similar results were obtained in a study carried out by Shuey and Cebel. They submitted 37 specimens of blood with a known content of glucose to 14 participating laboratories. In only one laboratory were as high as 92 per cent of the specimens reported correctly. In four laboratories, only 22 to 28 per cent of the specimens were reported correctly. Of a similar number of nonprotein nitrogen determinations of the blood, no laboratory reported more than 83 per cent correctly and one laboratory reported only 8 per cent of the specimens correctly.

When laboratory studies fail to confirm or perhaps run directly counter to carefully made clinical observations, the work of the laboratory must be checked to make certain that correct results are being obtained.

LACEY, A. H. *(Insulin Committee Lab., Univ. of Toronto, Canada):* A comparison of preparations of NPH insulin. J. Pharmacol. & Exper. Therap. *105*:196-202, June 1952.

The comparative activity of six preparations of NPH insulin, the products of four different laboratories, was determined in rabbits by means of a six-hour blood sugar method. They were found to exhibit differences in activity of small magnitude. These differences might be anticipated from small uncontrollable differences in insulin content; it appears reasonable to assume that nonbiological tests of NPH insulin provide adequate means of insuring constancy of the preparation from batch to batch.

LANDESMAN, ROBERT; DOUGLAS, R. GORDON; AND SNYDER, STUART S. *(Cornell Univ. Med. Coll. and New York Lying-In Hosp., New York City)*: Retinal changes in the toxemias of pregnancy. II. Mild and severe hypertension, renal disease, and diabetes mellitus. Am. J. Obst. & Gynec. *63*:16-27, January 1952.

In diabetes mellitus with associated toxemia, retinal vascular changes are a more ominous prognostic sign to the fetus than in toxemia alone. Changes in the arterioles graded 2 usually indicate death of the fetus unless early intervention is undertaken. Diabetic retinopathy is a further hazard to the vision of the mother; it tends to increase during pregnancy and may seriously involve the macular area. Patients with these findings should not attempt pregnancy. The frequent examination of the retinal vascular bed has been an important aid in the diagnosis, evaluation, and management of the toxemias of pregnancy.

LAURENCE, D. R.; AND STACEY, R. S. *(Dept. of Therapeutics, St. Thomas's Hosp. Med. Sch., London):* Effect of hexamethonium on the response to insulin in animals and man. Brit. J. Pharmacol. 7:255-60, June 1952.

The effect of hexamethonium on insulin hypoglycemia in man and in rabbits has been examined. Hexamethonium, 1) potentiates the convulsant action of insulin by increasing the degree of hypoglycemia, 2) abolishes or markedly alters the symptoms of insulin hypoglycemia in man, and 3) modifies the electroencephalographic changes in hypoglycemia. The relation of these effects to sympathetic blockade is discussed. The blood sugar level at which insulin convulsions develop is not affected by hexamethonium. Attention is drawn to the possibility of symptomless hypoglycemia occurring when insulin and hexamethonium are used together.

LAWRENCE, R. D. *(Diabetic Association, London):* Hypoglycemia in road users. Lancet 2:489, September 6, 1952.

Motor accidents have very rarely occurred because of hypoglycemia in diabetics who are taking insulin. Hypoglycemic attacks may arise from several causes, such as omitting to eat the necessary carbohydrate at the usual time. If the carbohydrate is either omitted or delayed, a severe reaction may occur owing to unopposed overaction of the insulin. The medical advisory committee of the Diabetic Association therefore asks all doctors looking after diabetics who take insulin and drive motor cars or ride motor or pedal cycles to make certain that their patients understand the possible causes of hypoglycemic attacks and how they can be prevented by regular intake of carbohydrate at the usual meals, which should be taken punctually. The committee especially hopes that, if a doctor knows that a patient sometimes does not recognize the symptoms of hypoglycemia, he will advise his patient not to apply for a driving license.

LEVY, EDWIN M.; DELL CORT, A. P.; AND LOGAN, VICTOR P. *(V. A. Hosp. Canandaigua, N. Y., and Dept. of Med., Univ. of Rochester Sch. of Med., and Dentistry, Rochester, N. Y.)*: Gastric acid response to massive doses of insulin: I. Prolonged observations on one individual. Gastroenterology *21*:547-50, August 1952.

Observations of the level of gastric acidity after large and varying doses of insulin were made on a single individual during a course of insulin shock treatment. Large variations were noted in acid values from day to day under apparently identical conditions. No clear relationship was found between the acid response and the level of hypoglycemia, the dose of insulin, or the degree of clinical insulin shock. Neither massive doses of insulin nor profound hypoglycemia inhibited the

parietal cell response. No exhaustion of the parietal cells was noted after this prolonged stimulation.

LJUNG, OLOF *(Med. Dept. of Centrallasarettet, Karlstad, Sweden):* Recrystallized insulin in insulin allergy: With report of a case of insulin resistance with local and general allergic reactions. Acta medica scandinavica *143*:260-65, July 8, 1952.

In a 61-year-old patient, amorphous commercial insulin and insulin recrystallized once produced local and general reactions. Insulin recrystallized seven times produced no local or general reactions. Insulin recrystallized seven times produced no local or general urticaria, but it produced a positive intracutaneous test. After eight months of therapy with insulin recrystallized seven times, there were no allergic reactions to any form of insulin.

LOPIS, S.; BOTHWELL, T. H.; AND SWERDLOW, J. *(Dept. of Med., Univ. of the Witwatersrand, and the Johannesburg Gen. Hosp., Johannesburg)*: Insulin-resistant diabetes; report of a case with an associated interstitial cell tumor of the testis. South African M. J. *26*:681-84, August 23, 1952.

The major interest of the case described in this paper was the finding of an associated interstitial cell tumor of the testis at autopsy. It is not clear whether this was causally related to the development of insulin resistance. It produced no obvious signs or symptoms and was not diagnosed during life.

From experimental evidence, it would seem that estrogens may have some protecting action against the development of diabetes, whereas androgens may increase the severity of the disease. For this reason, interstitial cell tumor of the testis, which may secrete androgens, has been included in the author's classification of insulin resistance.

LUECK, ARTHUR G. *(Des Moines, Iowa):* Arteriosclerosis as seen in diabetics. J. Iowa M. Soc. *42*:524-31, November 1952.

A series of 200 consecutive, unselected diabetics was studied at the time of routine office checkups for evidence of vascular degenerative changes. Albuminuria occurred more frequently in case of severe diabetes in which insulin was required. Those neuropathic changes, presumably due to insufficiency of the vasa nervorum, seem to occur oftener in cases of servere diabetes and in those not ideally controlled. Aside from these small differences, no serious damage to the vascular system appears to result from inability to maintain a normal blood sugar and a sugar-free urine.

LUISI, ANTONIO *(Rio de Janeiro):* Fatal hypoglycemic coma due to adenomas of the pancreatic islands. La presse médicale *60*:51-54, January 16, 1952.

The author describes a case of fatal insulin coma provoked by multiple adenomas of the pancreatic islands, the first case of this type reported in Brazil. The patient had convulsions, loss of consciousness, and atypical psychic manifestations and had been pronounced hysterical. The patient had had these attacks for more than ten years. Diagnosis was made at autopsy. The findings were four adenomas of the pancreatic islands, with almost absolute predominance of beta cells; acute encephalic edema; cerebral edema; and granulomatous lesions in the spleen, apices of the lungs, and lymph nodes.

LYNCH, FRANCIS W. *(Div. of Dermatology, Univ. of Minnesota):* Pruritus vulvae as seen in dermatological practice. J.A.M.A. *150*:14-18, September 6, 1952.

A diagnosis of pruritus vulvae is incomplete until other dermatoses, particularly psoriasis, have been considered. Any infection that may be present should be evaluated and treated more or less specifically. Certain etiological factors may be suggested by the duration and the appearance of the eruption. Treatment is fairly obvious if one finds diabetes, vaginitis, or other local abnormality. Endocrine factors are often apparent, but estrogenic therapy seems of little value; it may be used when premenopausal or climacteric symptoms are present and may alleviate tension, thus indirectly helping the pruritus vulvae.

Sedation can be a valuable aid, reducing irritability and anxiety and helping the patient toward emotional readjustment and suitable changes in interpersonal relationships. Atopy is frequently evident, but the author has no faith in "allergic management" of these patients. He is not encouraged by what he has seen of tattoo, injection, vulvar resection, or neurosurgical attempts. These patients are best treated by general supportive and hygienic measures, intelligent and cautious topical

therapy, limited use of roentgen therapy, and a superficial, nonspecialized "family doctor" type of psychotherapy. Removal or treatment of a single cause does not assure a cure; additional factors must be searched for and attacked when progress is not continuously favorable.

MACKENZIE SHATTOCK, F.; AND MICKLEM, LORNA P. *(Clin. Res. Unit, Three Counties Hosp., Arlesey Beds, England):* Insulin hypoglycemia and the eosinophil count. Lancet *1*:1239-41, June 21, 1952.

When insulin treatment is given for mental illness, the majority of patients after the first week show a rise in the resting level of the eosinophil count. After repeated hypoglycemic comas, the eosinophil count is likely to be significantly higher than at the start of the treatment. That repeated hypoglycemia increases the activity of the bone marrow is suggested by a rise in the resting level of the eosinophil count, by the occurrence of neutrophilia, by a left shift in the peripheral neutrophil count, and by a preponderance of immature eosinophil cells in the bone marrow.

MACKLER, BRUCE; MITHOEFER, JAMES; GRAUBARTH, HARRY; AMMENTORP, PETER; AND GUEST, GEORGE M. *(Hosp. Res. Found. and of Pediat. and Sur., Univ. of Cincinnati, Cincinnati):* Glucose utilization in acidotic hepatectomized dogs and eviscerated dogs. Am. J. Physiol. *169*:561-64, June 1952.

In hepatectomized dogs and in eviscerated dogs with and without severe acidosis induced preoperatively by intravenous perfusions of ammonium chloride, the disappearance of sugar from the blood was uniformly slower in acidotic than in nonacidotic states.

Whereas in hepatectomized, nonacidotic dogs (with pancreas intact) the rate of disappearance of sugar from the blood was accelerated after intravenous injections of glucose, in acidotic dogs the rate was the same before and after glucose administrations; thus, acidosis appears to interfere either with the action of insulin or with its production that normally follows glucose injections.

Acidosis inhibits the uptake of glucose by extrahepatic tissues, as demonstrated in experiments in which the effect and production of insulin were excluded by evisceration.

MARR, WILLIAM G. *(Dept. of Ophth. and Pediat. of the Johns Hopkins Univ. and Hosp.):* Cataracts and retinopathy in juvenile diabetics. Am. J. Ophth. *35*:577-82, April 1952.

Diabetes in juveniles causes two general types of cataract. In both types the cataract is bilateral, although the opacity may be more advanced in one eye than in the other. A cataract may develop rapidly (in a matter of weeks or less) in a young diabetic. By rigorous therapy these rapidly developing opacities may be greatly reduced or eliminated completely.

Most of the cataracts occur early in the disease and are rarely first diagnosed after five years of diabetes. Careful regulation of diabetes mellitus in juvenile patients undoubtedly reduces the incidence of cataracts, since their development is correlated with poor control of the disease. In the development of retinal lesions characteristic of retinopathy, the duration of the diabetes is paramount.

MCARTHUR, J. W.; CHAO, D. H. C.; MACLACHLAN, E. A.; MORRILL, M. F.; CAMPBELL, A. M.; WOOD, M. D.; ZYGMUNTOWICZ, A.; GOETZ, F. C.; AND SVEINSSON, S. L. *(Mass. Gen. Hosp., and Dept. of Pediat., Harvard Med. Sch., Boston):* A metabolic study of a diabetic patient: The effect of variations in the dosage of insulin upon adrenal cortical activity and upon water electrolyte and nitrogen excretion. J. Clin. Investigation *31*:592-97, June 1952.

A study was designed to determine whether there was a relationship between the degree of control of blood sugar and the level of adrenal cortical activity. A patient with mongolism and diabetes mellitus was given crystalline insulin in dosage levels ranging from 25 to 80 units for periods of 15 days while he was maintained on a constant diet and unlimited fluids. Dosage levels were selected which would permit a) maximal glycosuria without ketonuria, b) moderate glycosuria, c) aglycosuria with hyperglycemia, and d) normoglycemia. The level of adrenal cortical function was estimated by means of serial eosinophil counts and urinary corticosteroid determinations, and the rates of urinary excretion of nitrogen, sodium chloride, and potassium were also measured.

The dosage of insulin was found to exert a significant influence upon the rate of corticosteroid excretion, upon the eosinophil count, and also upon the rates of excretion of water, electrolytes, and nitrogen. The administration of large doses of insulin in attempts to insure continuous normoglycemia resulted in the occurrence of frequent

insulin reactions and in measurable increases in the rate of corticosteroid excretion. The administration of small doses which just prevented ketonuria exerted no detectable effect upon the rate of corticosteroid excretion or the eosinophil count, although a heavy glycosura ensued.

MILLER, JAMES W. *(Mason Clinic, Seattle):* Conservative and prophylactic surgical management of foot lesions in the diabetic. J.A.M.A. *150*:850-51, November 1, 1952.

In the author's experience, the infectious element seems to predominate in the majority of foot lesions in the diabetic. Vasospasm in usually not a prominent feature. Sympathetic interruption medicinally or surgically therefore has not been considered of much value, nor has the author used it widely. The new proteolytic enzymatic products have been used and offer definite promise as additional adjuncts in the conservative treatment of infectious and gangrenous processes. In the author's opinion, anticoagulants have rather limited use. The physician who will adhere to common surgical principles and administer the appropriate antibiotics has at hand the tools to approach many of these problems conservatively.

MILN, D. C.; AND BARCLAY, T. H. C. *(Glasgow Royal Infirmary, Glasgow, Scotland):* Acute colonic obstruction due to pancreatitis. Lancet *2*:168-69, July 26, 1952.

The secondary involvement of contiguous viscera from inflammation of the pancreas has often been described, but it is uncommon for the secondary condition to be so severe that the primary cause is completely masked. The two cases reported here exhibited an almost identical clinical feature, no feature of which, even at the first operation, suggested that the pancreas was at fault.

MINTON, JOSEPH: Ocular manifestations of diabetes. Med. Press *114*:127-35, February 6, 1952.

The diabetic patient develops sclerosis of the larger retinal capillaries which causes stasis with consequent formation of microaneurysms, retinal hemorrhages, and engorgement of the retinal veins. Sudden changes in a refractive error and in accommodation may be early symptoms of diabetes; later there may be cataract, glaucoma, retinitis proliferans, and blindness.

MOORE, FRANCIS D.; HALEY, HAROLD B.; BERING, EDGAR A., JR.; BROOKS, LAURA; AND EDELMAN, ISIDORE S. *(Depts. of Surg. and Med., Peter Bent Brigham Hosp., and the Dept. of Surg., Harvard Med. Sch.):* Further observations on total body water. II. Changes of body composition in disease. Surg., Gynec. & Obst. *95*:155-80, August 1952.

Alteration in fat content is probably the most important single variable, other than disease, that determines body water content. During weight loss, changes in total body composition may involve widely variant changes in total body water (both absolute and relative), in body fat, and in fat-free solids. Even when the human body is considered merely as a tripartite system of fat, lean tissue, solids and water, it is clear that a significant series of composition changes occur in response to disease. It is an interesting feature of fat oxidation that the organism, finding itself deficient in dietary calories, is apparently unable to use fat fast enough to provide calories for all its needs. The body resorts to gluconeogenesis (from tissue protein), with the familiar combination of fat loss with negative nitrogen balance. A mixed loss therefore occurs during starvation instead of the loss of fat alone, although fat loss may predominate. When a factor such as immobilization or an endocrine factor such as puberty, the menopause, or diabetes is added to the equation, then a more rapid deposit of body fat may occur.

MORGANS, MARGARET E. *(Med. Unit, Univ. Coll. Hosp. Med. Sch. London):* A comparison of plasma inorganic phosphate levels in normal and diabetic pregnancies. J. Endocrinol. *8*:242-44, July 1952.

No significant difference was found between fasting normal and diabetic subjects. The maternal values were similar in all groups except in the group of normal individuals delivered naturally, which was significantly lower than in cesarean cases and in fasting nonpregnant normal subjects. It seems that this low level is best explained as a physiological response to frequent glucose drinks during labor. This low level was not seen in the diabetic pregnancy terminating naturally, probably because the diabetic subject was unable to respond in a normal manner to ingested glucose. The cord values were the same in all groups even when maternal values differed significantly. The normal values obtained in the maternal and cord blood of diabetic mothers does not suggest an overproduction of growth hormone. It might be argued that the hormone therapy some patients re-

ceived played a part in suppressing the maternal pituitary and therefore resulting in normal phosphate levels. If this were so, the large size of the babies in this series would have to be explained on some other grounds.

NADBATH, RUDOLPH P.; AND FAUTEUX, LOUIS Z. *(U. S. Nav. Hosp., Portsmouth, Va.):* Diabetic lipemia retinalis. U. S. Armed Forces M. J. *3*:319-22, February 1952.

Lipemia retinalis, is not a common condition. There appears to be a greater incidence among women than among men. The association of the disease with diabetes has been attributed to the increase in blood lipid constituents which characteristically occurs in acidosis and coma. The pathogenesis of lipemia retinalis is not clearly understood. The blood lipids are maintained in solution by the phospholipid fraction, a depletion of which allows the other lipid fractions to separate from the blood, with the formation of the typical milky serum. It may be reasoned that, because of the deranged metabolism of fat which occurs in the liver in uncontrolled diabetes, the synthesis of lecithin is impaired, with the result that the blood phospholipid is diminished below the level at which the other lipids are maintained in solution. The changes in the fundus are pathognomonic. The retinal vessels appear light pink, salmon, waxy, or entirely white in color, as if filled with milk. Once insulin therapy is instituted, the prognosis in these patients is, in general, the same as the prognosis of any diabetic in or near coma; however, indiscretions or intercurrent infections are disastrous for the diabetic who has shown or is showing signs of lipemia retinalis.

NARDI, GEORGE L. *(Harvard Med. Sch., Massachusetts General Hosp., Boston):* Metabolic studies following total pancreatectomy for retroperitoneal leiomyosarcoma. New England J. Med. *247*:548-50, October 9, 1952.

Total pancreatectomy was carried out as part of a radical excision of a retroperitoneal leiomyosarcoma. The patient survived for one year. The "brittle" type of diabetes developed; only 20 units of insulin were required daily. There was no fatty infiltration of the liver. Radioactive phospholipid studies suggest that absence of the pancreas in man does not result in abnormalities of phospholipid metabolism as reported in dogs. The patient's nutritional status was better without pancreatin than with it. Serum amylase and lipase were repeatedly present in normal concentrations after total pancreatectomy.

NEWMAN, HENRY W.; WILSON, ROGER H. L.; AND NEWMAN, EDITH JR. *(Dept. of Med. Stanford Univ. Sch. of Med., San Francisco):* Direct determination of maximal daily metabolism of alcohol. Science *116*:328-29, September 26, 1952.

Study of four human, subjects, 32, 39, 44, and 66 years of age, of varying body build—two moderate drinkers and two chronic alcoholics—demonstrated a maximum metabolism of alcohol of 760 ml. of 100-proof liquor per day.

OGILVIE, HENEAGE *(London, W.1.):* Pancreaticogastrostomy. (Correspondence) Lancet *2*:388, August 23, 1952.

The author points out that it is difficult to see how any partial resection of the stomach, however extensive, could get rid of the gastric hydrochloric acid unless the vagus nerves were resected at the same time.

PASSWEG, EMIL: Pyroracemic acid in children under normal and pathological conditions. Am. J. Dis. Child. *84*:254, August 1952 [Abstr. from Ann. paediat. *175*:135, July-August 1950].

The content of pyruvic (pyroracemic) acid in the blood was determined in healthy children as well as in children with various illnesses of infancy and childhood. The normal value of pyruvic acid was found to be 0.69 mg. per 100 cc. Pathologic values were found in uncontrolled diabetes (maximum, 3.2 mg. per 100 cc.), in severe gastroenteritis (maximum, 2.8 mg. per 100 cc.), in acidotic vomiting (maximum, 2.4 mg. per 100 cc.), in toxic influenza cases (maximum, 1.8 mg. per 100 cc.), in hypochloremic states (maximum, 1.6 mg. per 100 cc.), after inanition (1.5 mg. per 100 cc.), in some chronic illness with very bad general health (maximum, 2 mg. per 100 cc.), and in a case of sleeping-drug poisoning after prolonged vomiting (2 mg. per 100 cc.).

PIHL, A. *(Nutrition Res. Inst., Univ. of Oslo, Norway):* Cholesterol studies: Dietary cholesterol and atherosclerosis. Scandinavian Journal of Clinical & Laboratory Investigation *4*:122-33, 1952.

In order to correlate the observed reduction in the mortality rate from cardiovascular disease in Norway

during World War II with the concurrent dietary changes, calculations have been made of the cholesterol consumption before and during the war. The calculations have been based on previous household studies carried out in Oslo. It was found that the cholesterol consumption was reduced from roughly 580 mg. per man value per day during 1936-1937 to 300 to 400 mg. per day during the war years. In 1941—when the death rate from cardiovascular disease was already distinctly below the prewar level—the cholesterol consumption was only insignificantly reduced.

The finding that the cholesterol intake was only moderately reduced, in spite of strongly decreased consumption of eggs, meat and meat products, milk, cream, cheese, and margarine, is explained by the following facts: During the war years, appreciable quantities of cholesterol were supplied by the increased consumption of fish and fish products and cod liver oil. Furthermore, the margarine had a considerably higher cholesterol content than in the prewar years since it contained higher proportions of cholesterol-rich herring oil. It is pointed out that the amount of cholesterol synthesized in the body is considerably larger than the quantities ordinarily consumed, and reference is made to recent tracer experiments demonstrating the sensitivity of the endogenous synthesis to variations in the cholesterol intake. In view of the efficient regulation of cholesterol metabolism, it appears unlikely that the reduced cholesterol intake during the war years can account for the observed reduction in the mortality rate. Available evidence indicates that the endogenous regulation of cholesterol metabolism and the level of fat and caloric intake may be more important in this respect than differences in the level of cholesterol consumption.

PIHL, A. *(Nutrition Res. Inst., Univ. of Oslo, Norway):* Cholesterol studies: The cholesterol content of foods. The Scandinavian Journal of Clinical & Laboratory Investigation *4*:115-21, 1952.

A series of cholesterol analyses of Norwegian foods is presented, and the importance of various foods as sources of cholesterol is discussed. Attention is called to the fact, frequently overlooked, that lean meat, fish, and fish products are important sources of cholesterol. If a truly low cholesterol diet is desired, animal products must be almost excluded.

PINCUS, I. J. *(Dept. of Physiol. Jefferson Med. Col., and the Dept. of Gastroenterology, Graduate Sch. of Med. Univ. of Pennsylvania, Philadelphia):* The hyperglycemic factor of the pancreas. Tr. New York Acad. Sc. *14*:319-21, June 1952.

For almost 30 years, it has been known that certain pancreatic extracts contain, in addition to insulin, a substance which can elevate blood sugar. The purpose of this paper is to discuss briefly certain aspects of this problem and to speculate on possible clinical and other implications. Although extensive studies have been performed in recent years, it has not been conclusively shown that this substance functions physiologically nor that it is derived from the alpha cells. A considerable body of evidence, however, suggests that both are true. Many more observations are in order, and many more studies must be made. Pancreatic extracts should be prepared and assayed for insulin and HGF content in patients with different types of diabetes and other conditions. Suitably prepared tissues should be carefully studied for alpha and beta cell relationships. This should be a fruitful field of investigation.

PIRART, J.; AND DESNEUX, J. J. *(Belgium):* Two cases of cancer of the pancreas simulating chronic pancreatitis and idiopathic sprue. Acta gastro-enterologica belgica *15*:99, 1952 [Abstr. from Surg., Gynec. & Obst. *95*:357, October 1952].

The authors report a case of benign diabetes associated with steatorrhea and emaciation in a 67-year-old man. Icterus, a worsening of the diabetes, and a palpable gall bladder indicated surgical exploration. A carcinoma of the pancreas was found. The authors also report the case of a 59-year-old woman with steatorrhea. The laboratory findings were classically those of sprue. A remission of several months followed a sprue regimen. When she returned, a large mass was palpable. She died with a large carcinoma of the pancreas which had developed in 3 years without icterus, without diabetes, and almost without pain.

PRYOR, WILLIAM D. *(Duke Univ. Sch. of Med., Durham, N.C.):* The pupillary changes associated with diabetic neuropathy. North Carolina M. J. *12*:605-07, December 1951.

A variety of changes in pupillary size and reactions may occur in diabetic neuropathy. Not infrequently, typical

Argyll Robertson pupils are seen in the absence of any other clinical or laboratory evidence of neurosyphilis. More care in examining the pupils and in looking for the characteristic fundal changes in diabetic patients would probably reveal an even greater incidence of minor ocular changes in the course of diabetic neuropathy. It should also be pointed out that the presence of Argyll Robertson pupils and the absence of knee jerks and ankle jerks cannot be taken as unequivocal evidence of neurosyphilis, since such a combination may occur in diabetic neuropathy.

QUERIES AND MINOR NOTES *(Horse Shoe, N. C.):* Reducing diet for hypoglycemic patients. J.A.M.A. *149*:1174, July 19, 1952.

The diet for an overweight patient with spontaneous hypoglycemia should be low in carbohydrate and high in protein, with a limited amount of fat. Fruit or fruit juices should be taken for breakfast, every two or three hours between meals, at bedtime, and, if awake, during the night. It is particularly important to eliminate sweets and cane sugar products of all kinds, since they stimulate the secretion of insulin and are therefore harmful. Beer and all other alcoholic beverages, when used regularly or in excessive amounts, because of their effect on the liver, cause spontaneous hypoglycemia; total abstinence is advisable in cases of hypoglycemia.

REVIEWS (SINGER, CHARLES) *(England):* History of diabetes. Brit. M. J. 2:654, September 20, 1952.

This is a review of a recent book by N. S. Papaspyros, entitled *The History of Diabetes Mellitus.*

RICHARDSON, ALFRED W.; LOMAX, DONALD H.; NICHOLS, JOHN; AND GREEN, HAROLD D. *(Depts. of Physiol. and Pharmacol., Bowman Gray Sch. of Med., and Physiol. Dept., Sch. of Med., Indiana Univ.):* The role of energy, pupillary diameter, and alloxan diabetes in the production of ocular damage by microwave irradiations. Am. J. Ophth. *35*:993-1000, July 1952.

Microwave-induced opacities are due both to increased ocular temperature and to a disturbance of the dynamic metabolic equilibrium of the lens, which may explain the latency of cataract formation following excessive microwave exposures. In the presence of alloxan-induced diabetes, 33 per cent of the animals in a series developed lenticular opacities in the irradiated eye within two to 15 days of exposure to energy previously found subdamaging alone. This energy was less than energies found subdamaging with less severe diabetes.

RICHARDSON, JOHN S. *(London):* The treatment of maternal obesity. Lancet *262*:525, 1952 [Abstr. from Surg., Gynec. & Obst. *95*:363, October 1952].

The present report is concerned with 40 women who developed obesity during or immediately after pregnancy. None of these women had glycosuria, and the sugar tolerance curves obtained in a few of them were all normal. The babies of women with maternal obesity were larger than those of the controls. The number of stillbirths was higher.

ROBINSON, F. A.; AND FEHR, KITTY L. A. *(Res. Div., Allen and Hanburys Ltd., Ware, Hertfordshire, England):* Estimation of protamine and insulin in protamine zinc insulin. Biochem. J. *51*:298-303, June 1952.

Insulin can be separated from protamine by paper chromatography developing with the upper phase of a mixture of n-butanol, glacial acetic acid, and water (3:1:4 by volume). A dye such as bromocresol green is used for locating the zones. The concentration of protamine and of various proteins in a solution can be estimated on filter paper by retention analysis with a suitable dye, e.g., erythrosin. The area of the unstained wedge formed above the protein spot is proportional to the amount of protein present. The method can be used to estimate the amount of protamine in protamine zinc insulin after removal of insulin by paper chromatography. The concentration of insulin in protamine zinc insulin can be estimated, after the insulin is separated from protamine by paper chromatography, by staining with bromocresol green solution, eluting the insulin-dye complex, and comparing the color of the eluate with that given by a standard solution of insulin treated in the same way. Data are recorded on the composition of a number of suspensions of protamine zinc insulin and on the distribution of the components between the phases of the suspension.

ROSS, PHILIP H.; AND GIBSON, MARTHA *(Waco, Texas,*

and Manteno, Ill.): Group diabetic management in a state mental hospital. Illinois M. J. *102*:196-201, September 1952.

A system of diabetic management in a large group of mental patients is described. First, a diabetic control physician should be appointed in the institution. He should be specially qualified in the field of diabetes and diabetic therapy. Second, a blood glucose determination should be made routinely on admission. Third, those nurses and attendants who will assist in this problem should receive some briefing on this subject. Such briefing should include an understanding of diabetes as a disease as well as instruction in technical details which they will be called upon to perform. By these methods, a small number of trained personnel can very adequately control large numbers of diabetic patients under difficult circumstances.

SCHEINBERG, HERBERT; AND GITLIN, DAVID (*Dept. of Med. and Pediat., Harvard Med. Sch., and Children's Med. Center, Boston*): Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). Science *116*:484-85, October 31, 1952.

Because of the demonstration of abnormalities in copper metabolism in Wilson's disease and the fact that most, if not all, of the copper normally present in serum is bound to ceruloplasmin, the authors investigated this protein and found that patients with Wilson's disease have much less ceruloplasmin in their serum than normal subjects despite the fact that their copper levels may be either higher or lower than normal. The familial character of Wilson's disease suggests that it is another example of a pathologic condition related to a congenital deficiency of a specific plasma protein, such as is seen in hemophilia.

SECCO, CARLO: Cushing's syndrome, the syndrome of adaptation. Fracastoro *44*:61, 1951 [Abstr. from Surg., Gynec. & Obst. *94*:597, June 1952].

The author describes the case of a 57-year-old man with diabetes and hypertension in whom renal studies revealed a mass on the right side. The patient died with hypotension 12 hours after operation. An adrenocortical tumor was found, and it was believed to have been due to prolonged exogenous and endogenous stress. The role of stress in the production of adrenal hyperplasia and the concomitant clinical findings are discussed.

SHROPSHIRE, R. F.; GINSBERG, JACOB R.; AND JACOBI, MENDEL (*Cataract Inst., South Kortright, New York*): The nonsurgical treatment of cataract. Science *116*:276-78, September 12, 1952.

The authors report the regression to disappearance of controlled induced cataracts in rats by the parenteral administration of fishlens protein extracts. Preliminary clinical trials in a group of 14 patients resulted in appreciable subjective improvement in all after four injections, and a diminution of lens opacities was observed ophthalmoscopically after six or more injections. Biophysical studies in progress indicate tremendous differences between the proteins of the lens of the mammalian eye and those of fish lenses.

SMITH, JULLIEN L.; BEAL, JOHN M.; AND FROST, PEGGY (*Surg. Serv., Wadsworth Hosp., Vet. Admin. Center, and Dept. of Sur., Univ. of California Sch. of Med., Los Angeles*): Comparative utilization of intravenous invert sugar and glucose. Surgery *31*:720-23, May 1952.

The purpose of this paper was to investigate recent reports that the human being utilizes invert sugar and fructose administered intravenously more efficiently than glucose. The patients used in this study were adult males 20 to 50 years of age who had not been operated upon and who were not suffering from any obvious nutritional deficiencies. It was noted that the retention of both invert sugar and glucose increased as the period of infusion was lengthened from 2 to 6 hours. In all patients the retention of glucose was significantly greater than that of invert sugar. Although fructose appears to be converted to glycogen more rapidly than glucose, it has been demonstrated that after the oral ingestion of small amounts of fructose it appears in the urine despite the fact that the blood fructose level remains quite low. In order for fructose, which comprises half of invert sugar, to be retained to any appreciable degree, it would be necessary that it be removed from the circulation quite rapidly, presumably by conversion to glycogen, in order not to be lost in the urine. A greater quantity of reducing sugar appeared in the urine, which was collected over a 24-hour period, from patients receiving one-liter infusions of 10 per cent invert sugar than from those receiving 10 per cent glucose. This was true of both fasting and fed patients. The authors conclude that it is dubious that invert sugar or fructose is as well utilized by the human being as is glucose.

SNYDER, STUART S. *(Depts. of Surg. (Ophthal.) and Obst. and Gynec., New York Hosp.-Cornell Med. Center, New York City):* Retinal findings in pregnancy complicated by diabetes mellitus and toxemia. Am. J. Ophth. 35:831-36, June 1952.

Grade-2 arteriolar changes in toxemias of pregnancy associated with diabetes mellitus should warrant early termination of the pregnancy; if discovered in the first trimester, abortion may be indicated; if not noted until the third trimester, termination becomes necessary. If Grade-3 or Grade-4 eye-ground changes develop during the first trimester, therapeutic abortion is probably indicated. When Grade-3 or Grade-4 eye-ground changes are noted later, immediate interruption is necessary if the fetus is viable. The type and degree of the diabetes in this series does not seem to have as much effect on the fetal outcome as does the type and severity of the toxemia. From this small series of cases, it seems that earlier interruption of pregnancies complicated by diabetes and a toxemia will result in more living babies even though some will be premature.

SPECK, C. D., JR.; DROSS, R. L.; AND MENDELL, HENRY *(Dept. of Med., Baylor Coll. of Med., and Jefferson Davis Hosp., Houston, Tex.)*: The coincidence of tuberculosis and diabetes mellitus. New Orleans M. & S. J. 104:493-96, June 1952.

In this series of 205 diabetic clinic cases, 7 (3.4 per cent had pulmonary tuberculosis. Among 2,366 admissions to a tuberculosis hospital, 15 diabetics were found (0.63 per cent). Diabetics are predisposed to the development of tubeculosis only if the diabetes is uncontrolled. Since the prognosis of the tuberculosis diabetic is actually that of the tuberculosis itself, early diagnosis and adequate treatment of this disease are most essential. The clinical signs and symptoms of the disease are patently deceptive; therefore, annual chest x-rays are desirable on all diabetics and especially on those more vulnerable groups noted above.

SWEENEY, J. SHIRLEY *(Gainesville, Texas)*: The Sweeney diabetic foundation camp for diabetic children. J. Oklahoma M.A. 45:348-49, October 1952.

There are four barracks, each with showers, toilets, infirmary room, and drug treatment rooms. Each barrack houses 24 children. There are two for girls and two for boys. The camp is primarily for children who live in the 16 Southern States; however, no child has ever been turned down because of the geographic location of his home.

VACCARI, FRANCESCO; AND ROSSANDA, MARINA *(Dept. of Pharmacol., Univ. of Milan)*: The blood glycolysis during the alarm reaction and after adrenal hormones and ACTH treatment. Archives internationales de pharmacodynamie et de thérapie. 90:421-26, August 1952.

During the alarm reaction the blood glycolysis presents a phasic course: an initial accentuation, then a depression, and a final reversion to the normal state during the countershock phase. In very strong stresses, the phenomena of depression prevail. ACTH in a large dose induces a picture similar to a heavy stress. High doses of cortisone alone cause a strong rise of the glycolysis and of the glycemia. ACE and DOCA have no significant influence.

WACHSTEIN, M. *(Dept. of Pathology, St. Catherine's Hosp., Brooklyn)*: The production of experimental lesions in the pancreas. Tr. New York Acad. Sc. 14:313-15, June 1952.

A review has been made of the subject of the selective destruction of the beta cells of the Langerhans islands, with the subsequent production of permanent diabetes by various agents. Among these substances are alloxan, dehydroascorbic acid, and 8-hydroxyquinoline. Other agents, e.g., diethyldithiocarbamate, selectively damage alpha cells. Various experimentally induced conditions may cause a reversible change of beta cells, commonly called "hydropic degeneration." This is apparently due to the intracellular deposition of glycogen. Concerning the exocrine portion of the pancreas, ethionine, a supposed methionine antagonist, not only damages the kidney and the liver but produces extensive destruction of the pancreas. Complete restoration of this organ, however, will occur following the withdrawal of the drug. Finally, destruction of the pancreas in the mouse can be caused by certain strains of the Coxsackie virus.

WAUGH, JOHN M. (Mayo Clin.): Islet-cell tumors of the pancreas. S. Clin. North America 32:1079-86, August 1952.

The incidence of islet-cell tumors found at necropsy varies with the interest of the pathologist in small tumors of the pancreas. Nonfunctioning tumors and benign functioning adenomas are usually firm in texture and grayish pink and are demarcated fairly clearly from the normal pancreas if not actually encapsulated. Adenomas which are cytologically active or "borderline" are usually poorly encapsulated or demarcated but otherwise cannot be distinguished from the benign group on gross examination. Malignant islet-cell tumors are soft, brown or brownish red, hemorrhagic, and nonencapsulated, with gross evidence of centrifugal spread into the surrounding normal gland.

Hyperinsulinism is a condition produced by an excessive amount of insulin. It is characterized by attacks at irregular intervals, usually related to need for food. The symptoms are of vasomotor and nervous origin. The first diagnosis is usually epilepsy or alcoholism and a brain tumor may be suspected. During the attacks the concentration of sugar in the blood is low, and values from 4 to 58 mg. per 100 cc. of blood have been recorded. Because of the frequent necessity for carbohydrates for relief of the attacks, it is not unusual for considerable obesity to develop.

Hypoglycemia may result from disorders other than islet-cell tumor. The degree of hypoglycemia is usually not so great, although on occasions concentrations of sugar in the blood may be just as low as with the classical islet cell adenoma. Effort hypoglycemia caused by physical exertion is not uncommon. Acute hypoglycemia is not unusual among children if all carbohydrates are withheld after overindulgence by the child.

Surgical exploration for islet cell tumor should not be delayed beyond the period needed for proper preparation of the patient after the diagnosis is established.

WEITZNER, HERBERT A.; AND SNOWDEN, VERNON L. (*Dept. of Med., Permanente Hosp., Oakland, Cal.*): Insulin hypoglycemia in treatment of rheumatoid arthritis: Preliminary observations of eleven patients. Permanente Found. M. Bull. *10*:119-28, August 1952.

A method of treating rheumatoid arthritis by means of mild hypoglycemic reactions induced by insulin is described. The possible mechanisms of action are discussed.

WEITZNER, HERBERT A. (*Dept. of Med., Permanente Hosp., Oakland, Cal.*): The role of insulin induced hypoglycemia in the treatment of rheumatoid arthritis and certain other diseases. Permanente Found. M. Bull. *10*:112-18, August 1952.

Patients with rheumatoid arthritis, acute and chronic gout, serum sickness, giant urticaria, contact dermatitis, psoriasis, eczema, sleep paralysis, narcolepsy, and fatigue state were treated with insulin-induced hypoglycemia, and good results were obtained. It is suggested that these and other "diseases of adaptation" may be benefited by insulin hypoglycemia treatment. The action of insulin hypoglycemia probably takes place through the stimulus of the hypothalamus, which causes ACTH to be evolved endogenously.

WEITZNER, HERBERT A. (*Dept. of Med., Permanente Hosp., Oakland, Cal*): Giant urticaria successfully treated with insulin induced hypoglycemia. Permanente Found. M. Bull. *10*:157-58, August 1952.

Two cases of giant urticaria were treated with mild hypoglycemia, insulin-induced. Remission was brought about in both patients. Subjective relief of itching and marked diminution of swelling took place promptly. The treatment is described briefly.

WEITZNER, HERBERT A. (*Dept. of Med., Permanente Hosp., Oakland, Cal.*): Insulin hypoglycemia in treatment of gout: Preliminary observations on three cases. Permanente Found. M. Bull. *10*:129-35, August 1952.

Three cases of acute gout were treated with insulin-induced hypoglycemia (mild). Temporary remission resulted within a relatively short time. Relief of pain and diminution of swelling occurred within 4 to 24 hours.

WEITZNER, HERBERT A. (*Dept. of Med., Permanente Hosp., Oakland, Cal.*): Insulin hypoglycemia in treatment of narcolepsy with temporary improvement: A case report. Permanente Found. M. Bull. *10*:153-56, August 1952.

A case of severe narcolepsy was treated with mild hypoglycemia, insulin-induced with apparently good results.

WEITZNER, HERBERT A. (*Dept. of Med., Permanente Hosp., Oakland, Cal.*): Insulin hypoglycemia in treatment of psoriasis with temporary improvement: Two case reports. Permanente Found. M. Bull. 10:149-52, August 1952.

Two cases of psoriasis were treated by means of mild hypoglycemia, insulin-induced, and temporary remissions followed.

WEITZNER, HERBERT A. (*Dept. of Med., Permanente Hosp., Oakland, Cal.*): Serum sickness successfully treated with insulin induced hypoglycemia. Permanente Found. M. Bull. 10:136-48, August 1952.

In nine cases of serum sickness, one or two insulin-induced hypoglycemic reactions were promptly followed by complete remissions. The precipitating cause of the serum sickness in 7 cases was tetanus antitoxin; in 2, it was sulfonamides and penicillin.

WILHELMJ, C. M.; MCGUIRE, TERENCE F.; AND WALDMANN, E. B. (*Dept. of Physiol. and Pharmacol., Creighton Univ. Sch. of Med., Omaha, Neb.*): Stress of realimentation with protein or carbohydrate following prolonged fasting. Am. J. Physiol. 169:248-53, April 1, 1952.

Following prolonged fasting, realimentation with high-calorie diets constitutes a severe cardiovascular, gastro-intestinal, and general stress which is most pronounced with diets high in carbohydrate. From studies made on four dogs (two male and two female), it appears that realimentation following severe inanition should be started with small amounts of easily digested protein or carbohydrates; no immediate differences were noted between low maintenance level isocaloric high-protein or high-carbohydrate diets. Realimentation at a luxus level of food intake caused marked increases of blood pressure and heart rate, which were usually more pronounced with the high-carbohydrate diet. It appears that the increase in pulse rate and blood pressure during refeeding may constitute a very valuable index of the margin of safety in increasing the caloric intake.

WOLFE, S. M.; AND PASCHKIS, K. E. (*Jefferson Med. Coll., Philadelphia*): Excretion of formaldehydogenic steroids in diabetics. Metabolism 1:413-19, September 1952.

The excretion of formaldehydogenic steroids was studied in 42 diabetics. Twenty-five of these (59 per cent) showed abnormally low excretion values, less than 300 μg per 24 hours. In 10 cases (24 per cent) the excretion values were within normal range (300 to 800 μg per 24 hours). In several cases in which determinations were made in a phase of inadequate diabetic control (but without acidosis), the excretion values were higher than in a subsequent period of adequate control. Complications that would be expected to cause a rise in excretion of formaldehydogenic steroids, including pregnancy, failed to do so in diabetics. High excretion (more than 800 μg per 24 hours) was observed in seven cases, including two of Cushing's syndrome, three of possible pituitary involvement, and one of diabetic acidosis. In one case, no tentative explanation for the high excretion levels was found.

WOMACK, C. RAY; AND MOYER, JOHN H., JR. (*Nashville, Tenn., and Houston, Texas*): Glucose tolerance: III. Evaluation of four types of tests in a heterogeneous group of 71 subjects with glycosuria. Am. Pract. & Digest Treat. 3:479-86, June 1952.

Three-hour, one-dose oral (standard) and one-hour, two-dose oral (Exton-Rose) glucose tolerance tests were performed in 71 cases in which there was glycosuria in the absence of clinical symptoms of diabetes. Intravenous tests were carried out in 46 of these cases, and in 62 instances a postprandial blood sugar level was estimated following a standard meal.

Fasting blood sugar levels, per se, were unreliable criteria for determining the presence or absence of diabetes mellitus. The intravenous test under some circumstances may be more reliable, eliminating changes resulting from variable gastro-intestinal absorption, but may also cause mild diabetes to be overlooked. The standard test is simpler to perform and appears to give reliable information if gastro-intestinal absorption is normal. The one-hour, two-dose oral (Exton-Rose) test is excessively sensitive and unreliable and should be discarded as a diagnostic laboratory procedure. Glycosuria is a finding related to the renal ability to absorb glucose in glomerular filtrate. As a result of renal mechanisms, glycosuria may occur in individuals with no evidence of disturbed carbohydrate metabolism.

EDITORIALS

DECLINING MORTALITY IN OLDER PERSONS

Contrary to a widespread impression, the death rates among older persons in our population have shown marked improvement in the last two decades. This has been brought out in two recent reports.* Between 1930 and 1949 the death rate for white women in the United States fell 25 per cent at ages 65 to 74 years, and 20 per cent at ages 75 to 84. For white males the declines were smaller, but by no means negligible. All the factors responsible for the improvement have not been identified, but an analysis of the trends by cause of death is rather informative. Probably most significant has been the large reduction in the death rates from pneumonia and influenza. In both age groups (65 to 74 and 75 to 84) current rates are well under half those prevailing two decades ago. There have been sizable reductions in many other causes including tuberculosis, the late effects of syphilis, and several conditions frequently involving surgery. The death rates from cardiovascular-renal diseases have declined among white women in both age groups previously mentioned and among men at ages 75 to 84 years. Even diabetes has shown a downward trend in mortality at the older ages in recent years and the level of the 1948 death rates at these ages is back to the 1930 figure. There has been a substantial reduction also in the death rate due to accidents. Only cancer, among the major causes of death, has shown no decline.

Certainly the most direct and specific influence on the improved outlook for longevity in old age has been the development and wide use of the sulfa drugs and antibiotics. This has enabled old people, even those afflicted by chronic disease, to come through medical emergencies that they meet. These drugs have not only helped to control respiratory and other infections among them but have been instrumental in making surgery safer for them and have made surgeons less hesitant about undertaking even radical operations in older people. Numerous other medical advances have helped to prolong the lives of old people and to keep them healthy. Recent years have seen increasing attention paid to their medical and nutritional problems. They have been helped also by the extension and improvement of medical facilities and medical care.

Older diabetics have benefited by all of this and also by specific advances in the control and management of their disease. Thus, the marked reduction in the death rate from gangrene reflects both its declining incidence through control of diabetes and the greater skill and knowledge in caring for patients who develop gangrene. The reduction in mortality among older diabetics is substantial. Analysis of the experience of the Joslin Clinic indicates that at ages past 65 the death rates declined 20 per cent between the period 1926-28 and 1939-47. There is evidence, moreover, that older patients first coming under treatment in recent years have fared better than the patients of earlier years.

There is good reason to expect further gains in longevity at the older ages. It is altogether probable that people reaching this period of life in the years to come will be in better health than those who attained old age in the past. There is much still to be gained not only from diffusion of present knowledge and higher quality of medical care, but from medical research, so much of which is devoted today to the problems of aging.

HERBERT H. MARKS

* Robert J. Myers: Vitality of the Aged. Science. Vol. 116, July 18, 1952, p. 67. Improvement in Mortality Among the Aged, Stat. Bull., Met. Life Ins. Co., July 1952, p. 3.

DIABETIC NOSTRUMS AND QUACKERY

Responsible persons in both government and medicine have long regarded it as their duty to protect the public from medical quackery. The only means of so doing are public education and legal procedures aimed at restraining or punishing the purveyors of such misbranded remedies.

Governmental agencies and medical organizations should, and do, supplement each other in these activities. In the matter of education, both have done less than is needed. Specialized medical societies, such as those for diabetes, tuberculosis and cardiac disorders, because they publish literature for patients and their relatives and friends who are personally interested in particular diseases, have a unique opportunity not enjoyed by organizations which spread their educational efforts over the populace at large. Reaching highly selected audiences, these societies can expose specific fraudulent practices to those who will listen because they are directly concerned.

Respecting the restraint and punishment of charlatans and the suppression of their wares, the government has the ultimate responsibility. The Food and Drug Administration, the Federal Trade Commission, and the Post Office Department have been active in ferreting out violations of the law and bringing offenders to justice. Here again, however, the medical organization interested in a single disease can be of the greatest service in calling attention to undesirable situations of which it has special knowledge and which, because of their number and local character, might otherwise be overlooked by the federal authorities.

Since 1941 the American Diabetes Association has had a standing committee dealing with nostrums. This type of activity is now included in the duties of the Committee on Therapeutics. This committee contributes to public education by cooperating with the editors of the ADA FORECAST in dispelling popular illusions about the treatment of diabetes and in exposing fraudulent remedies and "cures". Questions addressed to the Association are referred to the committee. The chairman, acting either upon his own responsibility or upon the advice of his colleagues, provides the answers to these queries within the scope of the committee.

The appearance of new nostrums, and the resurrection of old ones, frequently are brought to the attention of the committee by its own members, who are scattered widely over the country for scouting purposes, and by other alert members of the American Diabetes Association. Information thus acquired is checked with the comprehensive files of the Bureau of Investigation and the Council on Pharmacy and Chemistry of the American Medical Association, with which the committee maintains a close liaison. The matter is then referred to the Food and Drug Administration, the Federal Trade Commission, or the Post Office Department, or all three, for action. Not uncommonly these agencies learn of a new nostrum for the first time through this committee. Committee members have testified, as individuals, in legal actions brought again unscrupulous manufacturers and distributors. The record of convictions in such cases is impressive.

The value of the Committee on Therapeutics stands in almost direct proportion to the diligence of physicians in reporting to it any obviously worthless treatment for diabetes which they may encounter.

HENRY T. RICKETTS, M.D., *Chairman, Committee on Therapeutics*

RECOVERY FROM RETINOPATHY

Spontaneous recovery from diabetic retinopathy is extremely rare. Improvement in vision of any degree is encouraging, but the complete disappearance of the objective evidence of retinopathy is of considerable significance. Poulsen's well-documented case report appearing in this issue of DIABETES, thus deserves special attention.

The significance of the observations in this case is two-fold. First, the complete reversibility of the pathological changes in the retina is demonstrated. Second, light is thrown on the etiology of the condition. The occurrence of Simmonds' disease preceded the spontaneous cure of the retinopathy. Thus hypofunction of the pituitary and presumably of the adrenal glands appeared to exert a beneficial influence in respect to the retinal condition. This rare accident, therefore, supports the theory first suggested by Becker that relative hyperfunction of the adrenal may be the precipitating cause of the retinopathy in diabetics.

In any case, solid evidence that recovery from diabetic retinopathy can occur should give great encouragement to all who are searching so eagerly for effective treatment and for means of prevention of this serious complication of diabetes.

JONAS S. FRIEDENWALD, M.D.

THE HEART IN HEMOCHROMATOSIS

In a recent paper, Swan and Dewar[1] called attention to those occasional patients with hemochromatosis in whom

cardiac symptoms and signs dominate the clinical picture. They reported two cases in one of which there was recurrent, prolonged, severe substernal pain with T-wave changes in the electrocardiogram consistent with a myocardial infarction. This patient recovered so that there is no definite evidence as to what part hemochromatosis played in the cardiac complication. In the second case, death from congestive heart failure occurred. Postmortem examination showed an enlarged heart weighing 400 gm., normal valves and coronary arteries and an intense, patchy siderosis of the myocardium with considerable destruction of muscle and replacement fibrosis.

In his monograph on hemochromatosis, unique in this field, Sheldon[2] concluded that myocardial failure was uncommon as a cause of death. However, in a review of the more recent literature, Swan and Dewar found a number of reports of cases of hemochromatosis in which there occurred symptoms followed by death in congestive heart failure. They summarized the findings in 14 of these. Among the 27 fatal cases occurring in the series of 30 patients with hemochromatosis reported by Marble and Bailey,[3] there were six whose death was attributed to heart failure, with or without coronary insufficiency or thrombosis. In the 15 of the 27 fatal cases in which postmortem examination was done, the heart muscle usually had a deep brown or reddish brown color. Coronary sclerosis was found in 7 of the 15 cases and at times was extreme. Microscopically, specific pigment granules were noted in the muscle fibers in 10 of 15 cases. The pigment tended to collect around the nuclei and in some the entire muscle cell was replaced by pigment granules.

Apart from the fact that voluntary and plain muscle are relatively free from involvement, the finding of large amounts of iron pigment and fibrosis in heart muscle is not surprising since it is common knowledge that in hemochromatosis there is usually widespread deposition of hemosiderin and hemofuscin throughout the body. However, it is not generally appreciated that in the occasional patient the deposition of iron pigment in the heart muscle may be so marked and the subsequent fibrotic response so extensive that a greatly weakened myocardium may result.

Of particular interest are the following clinical features: 1) The patients affected are usually not elderly, being below 60 and often below 50 years of age; 2) Symptoms of cardiac decompensation usually progress with relative swiftness; 3) Measures commonly employed in treatment such as rest, digitalis, low sodium diet and diuretics provide at most only temporary benefit. The course is usually progressively for the worse and death may take place within several weeks or a few months after the onset of definite cardiac symptoms. Consequently, whenever a diabetic patient in the fourth to sixth decades with hepatomegaly and skin pigmentation develops rapidly progressive congestive heart failure which does not respond to treatment in the usual fashion, then hemochromatosis with unusually severe involvement of the myocardium should be suspected.

ALEXANDER MARBLE, M. D.

[1] Swann, W. G. A. and Dewar, H. A.: The heart in hemochromatosis. British Heart Journal *14*:117-129, 1952.
[2] Sheldon: Hemochromatosis. London, Oxford University Press, 1935.
[3] Marble and Bailey: (Am. J. Med., *11*:590-599, November, 1951.)

SELECTION OF THE PRIZE STUDENT ESSAY ON DIABETES

The Editorial Board of DIABETES has been assigned the task of selecting the best paper submitted by a student or intern for the prize which will be awarded by the American Diabetes Association. It has already begun its work and will proceed with the appraisal of entries in the coming months.

As announced last summer, the prize of $250, donated by the St. Louis Diabetes Association, will be awarded to the author of the best paper on any subject related to diabetes. It can be a report of research, a biographical or historical note, a case report, or a review. Although entries will be accepted until April 1, it is hoped that a good share of the additional manuscripts will be submitted early since this will facilitate the work of the Board.

Members of the Association are invited to bring the prize to the attention of students and interns. An interest stimulated early in a medical career may yield important dividends in the development of the field in which we are all especially interested.

THE WRITINGS OF THOMAS WILLIS, M.D.

DIABETES THREE HUNDRED YEARS AGO

Frank N. Allan, M.D. BOSTON

Diabetes has been described in records dating back to antiquity, but the first important medical treatise on the subject in the English language appeared in the writings of Thomas Willis, published in 1679 under the title "Pharmaceutice Rationalis".

In the opening paragraphs, one finds presented the cardinal symptoms of diabetes, including the polyuria, the polydypsia, and the sweetness of the urine "as if there had been Sugar or Honey in it". It is interesting to read the details in the language of the time, presented under the book and chapter titles which follow:

PHARMACEUTICE RATIONALIS:

or,

An Exercitation of the Operations of Medicines in Humane Bodies. Shewing The Signs, Causes, and Cures of Most Distempers incident thereunto.

SECTION IV, CHAPTER III

OF THE TOO MUCH EVACUATION BY URINE AND ITS REMEDY; AND ESPECIALLY OF THE DIABETES OR PISSING EVIL, WHOSE THEORY AND METHOD OF CURING, IS INQUIRED INTO.

The Diabetes was a Disease so rare among the Ancients, that many famous Physicians have not so much as mentioned it, and Galen never knew above two that were troubled with it; but in our Age, that is given so much to drinking and especially to guzzling of strong Wine, we meet with very frequent, not to say daily examples and instances of this Distemper. But though it be familiar and its appearance well known among us, yet what are the causes and true nature of it, we are almost wholly to seek. Upon which, that I may venture to philosophize or rather give you my opinion, in the first place I shall lay down the description of this Distemper in all its circumstances, or the principal phaenomena (or appearances) of it; and then I shall

endeavor to find out, from what vitiated part or humour all those arise.

The Diabetes, so called from Diabaino (transeo, to pass through) is said to be a swift passing of the potulent matter (or drink) or a great flux of Urin. Such as are troubled with this Distemper, piss much more than they drink or take of liquid nutriment; and likewise they have a continual thirst, a lingering Fever, and as it were an Hectick always upon them. But as to what several Authors say, that the Drink is little or nothing changed, there is no truth in their assertion: because in all People (that I ever happened to know, and I believe it to be so in all) their Urin was very different, not onely from the Drink that they took in, but also from any other humours that are usually generated in our Bodies, being exceedingly sweet, as if there had been Sugar or Honey in it. The occasion of the aforesaid errour (I suppose) was from the colour of the Urin, which always looks crude and waterish, as in those that are troubled with the Green-sickness or Dropsie. To find out the reasons of these symptoms, let us inquire first, why the Urin is voided so copiously and so quickly, and then proceed to the remaining causes of the Distemper.

The clinical observations were fairly accurate, but the next section dealing with the etiology of diabetes shows how far astray were the speculations of those days. Willis disagreed with the common idea that the disorder originated solely in the kidneys (Reins). He thought that the trouble was mainly in the blood; the participation of the nervous system through the "nervous juice" was also postulated.

Whereas some assign, for the cause of a Diabetes, the attractive quality of the Reins, I do not like their reason; for the Bloud is not attracted to the Reins, but is driven thither by the motion of the heart. Nay farther, Neither doth the Serum seem to be drawn out of the Bloud whilest it runs through them, or to be, as it were, milked out, but to be separated partly by percolation, and partly by a kind of fusion or precipitation, as I have formerly and clearly shewn. Wherefore I hold that a Diabetes is rather and more immediately a Distemper of the Bloud than of the Reins, and that it takes its original from thence, in as much as the mass of Bloud doth as it were melt and is too copiously dissolved into serousness; which indeed is very manifest from that vast quantity and great augmentation of Urin, which cannot proceed but from the melting, as it were, and consumption of the Bloud. . . .

That therefore I may venture to tell you the immediate cause and true nature of the Diabetes, I am inclined to believe that the temper or mixture of the Bloud is so loosened, and in a manner dissolved, that the watery particles cannot be kept in by the thicker ones, but flying quickly out of their embraces, and being impregnated with salt ones, run out through the most open passages of the Reins. But in the mean time to dilute the Bloud, and keep it from curdling, other humours both from without and within too, are drawn to, and mingled with it, and the heart is put always into a far more violent motion.

Yet farther, I think that the Reins, also, sometimes are some part of the immediate cause, because their ferment uses oftentimes to be so vitiated, that it cannot keep the Bloud by the influx of its lixivial Salt in a due mixture and fluidity, in so much that as the Serum is separated from it by mere percolation; . . . But it is probable enough that copious pissing proceeds in some measure from the ill conformation or make of the Reins; . . .

Now that we have shown the immediate cause and true reason of a Diabetes, let us proceed to find out the procatarctical or more remote and original causes thereof. If therefore you inquire why the constitution of the Bloud grows so lax and dissolute, and apt to melt, as it were into Serum, I say, that the fusion of this, just as of Milk, proceeds from the meeting and associating of several kinds of Salt in the mass of it, whereby the other particles, being freed from the saline ones (that separate them from each other, and keep them in a due mixture) divide themselves presently into several parties. . . . Nor doth this Distemper proceed onely from things that we take in, but very often also from humours generated within. . . .

But for a principal share in this malady, we may justly bring in the nervous juice; for I have elsewhere shewn that this same juice, if ever it degenerates from its right temper, becomes very malignant and hurtful not onely to other humours, but to the solid parts: and that is the reason that from the depravation of this, the mixture also of the Bloud is very much in danger to be perverted. But that the nervous juice it self is perverted, we may conclude, because in a Diabetes the animal spirits are exceeding fainty, and all nourishment is immediately frustrated.

The possibility that Willis recognized diabetic neuritis is suggested by the paragraph which follows:

. . . I have observed in many People who have been

subject to this disease by intervals, that a little before they fell into such a flux of urin, they felt flying, running pains through their whole Bodies, and corrugations sometimes with dizziness or stinging, and other whiles with frequent contractions or convulsions, twingings of the tendons and other disturbances and restlessness of the spirits; which was a certain sign that the liquor which moistened the nervous fibers, being degenerated from its temper, and filled with dregs, did irritate or provoke the spirits, and force them into disorders. And then afterward, when the recrements and superfluities of the nervous juice, having gained a fluidity, ran out into the mass of bloud and caused a Diabetes, the aforesaid symptoms ceased, but then there ensued a languishment in the spirits, and a weakness all over the body.

The author finally attempted to leave theory to present further consideration of the clinical picture. However, he immediately returned to further speculation, without finding it possible to come to satisfactory conclusions. "Why it (the urine) should be so wonderfully sweet like Sugar or Honey is not easie to untie".

Willis was familiar with the variable and uncertain course of diabetes which makes prognosis difficult. He was also aware of the fact that treatment is easy when undertaken early. "But as to the Cure of it, it seems very difficult . . . to point out the true way of curing it". Nevertheless, he presented a lengthy discussion of therapy including a case report.

As to its prognosticks or fore-knowledge, this disease at first beginning is oftentimes easily cured; but when grown strong upon a man, very seldom and with great difficulty; in as much as the temper of the Bloud, being a little loosened, is reduced without much ado, but when it is much dissolved, so that most of its parts separate from each other, it is hardly or never to be restored.

But as to the Cure of it, it seems very difficult in this Distemper to point out the true way of curing it; for as much as the cause of it lies hid in such obscurity, and has an original so deep and remote. . . . Therefore in this Distemper, as in several others, there are three primary Indications or ways pointed out how to cure it; to wit: the Curatory, Prefervatory, and Vital. . . . Rice, White Starch, slimy Vegetables, and also Gums, and some resinous bodies are used to prove good in this Distemper.

. . . The Vital Indication is performed by thickning and moderately cooling Diet and by Cordials that are temperate, and especially by convenient and seasonable hypnoticks or sleeping Medicins, of which some of the chief sorts and choicest Receipts are laid down in the following Chapter, and in the end of this for a farewel I thought, fit to tell you the story of a certain nobleman who was sick of this Distemper, whilest I first meditated upon and afterward wrote this Discourse.

A Case Report

A certain noble Earl, renowned not onely for the splendor of his Birth, but for the extraordinary qualifications and endowments of his mind, being of a Sanguine temper, a florid complexion and in the very vigour of his Age, (though no body knows upon what occasion) became much inclined to excessive urination; and when for several Months he had been used ever now and then to make great quantities of water he at last (it seemed) fell into a diabetes that was obstinate and strong and almost desperate. For besides that in the space of 24 hours he voided almost a Gallon and a half of limpid, clear and wonderful sweet water, that tasted as if it had been mixed with Honey; he was likewise troubled with an extraordinary thirst, and as it were, an Hecktick Fever, with a mighty languishing of his spirits, weakness in his limbs, and consumption of his whole body.

When at this time I was sent for to consult with these excellent physicians Doctor Michlethwait, and Doctor Witherly, they had prescribed the following remedies by the use of which he in a short time seemed to grow well again.

Take of the Tops of Cypress viii handfuls, of whites of Eggs beaten together, two pints, of Cinamon ℥ ss, when you have cut them small, pour to them of new milk vii pints distil them in the common instruments, taking care that it burn not: and let the patient take ℥ vi thrice a day.

Take of Gum Arabick, and Gum dragant each ʒ vi of Peneds ℥ i make a Powder and let him take about ʒ i or ʒ iss twice a day with ℥ iii or ℥ iv twice a day with ℥ iii or ℥ iv of distilled water.

Take of Rhubarb pulverized gr. xv of Cinamon gr. vi make a Powder and let him take it in the morning, repeating it within six or seven days.

Take of Cowslip water ℥ iii, of Cinamon-barley water ℥ ii, of Syrup of Poppies ℥ ss make a Potion to be taken every night.

His Diet was only of Milk, which he took sometimes raw and diluted with either distilled or barley water and sometimes boiled with white bread, or barley, several times a day. By the use of these things growing daily better and better he seemed within a Moneth to be almost quite well: when he began to be pretty hearty, his Urin which was insipid, did not much exceed the quantity of that liquid matter which he took in: then afterward growing somewhat saltish it was less than what he drank till at last by degrees recovering his usual tenure of spirits and strength he returned to his former diet.

But yet the disposition to this Distemper did not so totally leave him but that afterward, oftentimes, through disorders in his Diet and perhaps irregularities in the seasons of the Year, being inclined to a relapse he made water at first in great quantities and then clear and sweet with thirstiness feverishness and languishment of his spirits. . . .

The Career of Thomas Willis

Thomas Willis was born in 1621, the son of a well educated land owner who lived near Oxford, England, according to an obituary published in the 1684 edition of his collected works. He attended Christ Church College in Oxford, graduating in 1639. The Civil War was then beginning. His father died "by an Contagion of a Camp-Feaver." He "betook himself again to Oxford, being the tents of the King as well as the Muses; where listing himself as Souldier in the University Legions, he received pay for some years; until the Cause of the best Prince being overcome Cromwells Tyranny afforded to this wretched Nation a Peace more cruel than any War. . . . In the meantime he writ and published those most excellent tracts by which he first became known to the world, viz. Of Fermentation, of Feavers and of Urines."

"At length the King restored and access opened to University Degrees and publick Employs he proceeded Doctor and was publickly declared (in 1660) Professor of Natural Philosophy, which profession he did adorn with the highest praise; moreover, his Anatomy of the Brain, and his Treatise of the Scurvy, and of Convulsions, were published.

"But about the year 1667, being called to London to practice Physick, it is incredible to relate how soon, and with what great Commendations he grew famous. . . ." Although he acquired the largest fashionable practice of the time, he continued to study and write extensively. "But though he spent whole days and nights in care of the sick, he was yet at leisure to adorn his Art by composing Books, from whence among a thousand interuptions he published these Treatises, of the Ascension of the Blood, and of Muscular Motion, of the Soul of Brutes, of the Diseases of the Brain. . . . "At length being near fifty-seven years of age, in the beginnings of November he seemed troubled with a cough (now the Epidemical Disease of the time) which (while it was thought light and inconsiderable) suddenly passed into Pleurisie and Pneumonia. And when this most expert person was not relieved by frequent Bleeding and diligent taking of remedies, himself perceived the period of his Life to approach . . . he commended his pious soul to God, having his senses entire to the last breath, and finished his most exemplary Life with the like death."

The writings of Willis appeared first in Latin. The collected works were translated by S. Pordage "out of the Latine into our Mother Tongue for the benefit of my Country-men." The first edition published in 1681 must have met with success; a second edition appeared in 1684 with "The Pharmaceutice new Translated and the Whole carefully corrected and Amended."

Pordage, a "Student in Physick," appears to deserve unusual credit. In the book he inserted a valuable table. "Since nothing could do so well express the meaning and intention of the Author as the very Latin and Greek words used in these tracts, we have continued them expressly," he said, "and though in many Places I have given their meaning by Synonyma's, yet for the benefit of meer English Readers we have composed a Table alphabetically of all the hard Greek and Latin words used in the whole volume. . . ." An examination of the table leads to interesting observations, including the definition of the pancreas, "called

in a Hog the Sweet bread. It is a remarkable kernel placed below the Ventricle, and serves for a division of the Vena porta, as also to defend the Ventricle from touching the back. . . . Ventricle, is the stomach, or that part which receives the meat and drink, being swallowed down, and which hath in it self the virtue of digestion."

The volume contains in the preface, a poem which may be quoted in conclusion. Although its meaning is obscure, it illustrates the scholarly mind of a medical writer of the 17th century.

The intricate and hidden cause of things,
Both Peace and Strife by what means Nature brings,
What various motions Bodies do inspire;
What mixes with the Waters quenchless Fire,
What Bonds the Elements together tye,
Before this happier Age unfolded lye:
Things hid to former Ages, and unknown,
The Secrets of the World to all are shown.

BOOK REVIEWS

TREATMENT OF DIABETES MELLITUS. By Elliott P. Joslin, A.M., M.D., Sc.D.; Howard F. Root, M.D.; Priscilla White, M.D., Sc.D.; and Alexander Marble, A.M., M.D.; New England Deaconess Hospital, Boston, Mass. Ninth Edition, throughly revised. Cloth. $12.00. Pp. 772 with 26 illustrations. Lea and Febiger, Philadelphia. 1952.

An assignment to review this book is something like an assignment to review the Encyclopedia Britannica. For the student of diabetes there is such a great wealth of information here, current knowledge is so fully recognized and treated, experience of the authors is so broad and organization so effective that there is little to say except that everything worth knowing is contained therein. No similar work can approach it in completeness and authoritativeness. With frequent and intelligent revision none may do so for a long time to come. Continuity in responsible authorship, under firm leadership, is the chief reason why this is true.

From the publishing standpoint the new (ninth) edition is a handsome job. The reasons for this are a rich, green cloth cover, more type area per page and lighter paper stock, so the book is noticeably thinner and easier to handle. There is more attractive type in paragraph and chapter headings. In comparison with the eighth edition, printed six years ago, it has a streamlined look but is easily recognizable as an old friend in new clothes.

The plan of organization of the contents remains the same. In sequence the background, incidence, na-

ture, characteristics and treatment of uncomplicated diabetes are described. These sections are followed systematically by thorough discussions of various complications and associated diseases, the four chief authors taking turns in assignment with assists in special fields by others in the group. One previous major author is now missing.

On the whole a thorough job of revision has been accomplished. There are few sections which do not show, at the very least, minor insertions, deletions and elaborations. This reviewer is impressed the most by several radical changes, all decidedly for the better. First, there is Dr. Marble's concise summary, to a large extent new, of the physiology of diabetes, the intermediate chemistry of carbohydrate metabolism, the action of insulin, endocrine relationships, and forms of experimental diabetes. Then there is the valuable new chapter of the pathology of diabetes by Drs. Shields Warren and Philip Le Compte. A beautiful page of colored microphotographs is included here. These authors shrewdly call attention to the possible role of the mucoproteins in the pathogenesis of vascular and renal complications of diabetes, as Dr. Root has done elsewhere.

The title of the book is too modest. Much more than the treatment of diabetes mellitus is described between its covers. The chapter on treatment has been rewritten in a more practical and simplified form. Good justification for seeking control of glycosuria and hyperglycemia as perfectly as possible is given convincingly by Dr. Joslin.

Dr. Root has brought the important section on vascular and renal complications of diabetes into current focus. Certainly the mechanism of their causation is as yet unknown, but a valuable service has been rendered by the fact that this competent and experienced authority has assembled most of the known facts in one place.

The section on skin disorders has been rewritten by Dr. Marble and that on urinary tract disease by Dr. Styron. Surgery in diabetic patients, the behavior of gangrene and its treatment, and Dr. McKittrick's indications and techniques for the important transmetatarsal amputation, by virtue of which many serviceable feet are now saved, are described in considerable detail.

Dr. White relates her experiences with diabetic children and pregnant women. She re-emphasizes the importance of hormonal imbalance in the production of high rates of fetal mortality and maternal toxemia, and of improvement in these rates by means of treatment with estrogens during pregnancy. She calls attention to the comparative mildness of the diabetes in other series in which fetal mortality and maternal morbidity have been low even without the use of hormones.

It is difficult to be critical of such a wealth of information recorded so faithfully. Some, including this reviewer, have felt that too free use of actuarial methods has detracted from the descriptive value of the study. Just because a group of diabetics shows given characteristics, on the average, it does not follow that every person in the group will exhibit these characteristics, of course. Yet one often gains the impression that the authors would have the reader believe that this is so. Probably this is only a method of teaching what the usual pattern is. Certainly no better teachers exist than these authors.

Dr. Joslin's group deserves the grateful thanks of all who are interested in diabetes. This precious accumulation of facts about the disease, the complete reviews of the literature to supplement personal observations and the conscientious revisions of the textbook periodically are contributions of lasting merit. No student of the disease can afford not to possess this newest version of a standard and now famous work.

DIABETIC GLOMERULOSCLEROSIS: *The specific renal disease of diabetes mellitus.* By Harold Rifkin, M.D., Louis Leiter, M.D., Ph.D., and James Berkman, M.D. $3.50 98 pp. Illustrated. Charles C. Thomas, Springfield, Illinois, 1952.

This small monograph of about 100 pages reviews the recent literature pertaining to diabetic glomerulosclerosis and details the clinical and laboratory findings in 44 cases diagnosed during life at the Montefiore Hospital in New York. The numerous illustrations are excellent. The tables are well organized, easily read and informative. The value of the book is enhanced by an alphabetically arranged bibliography and an index which includes both subjects and authors.

The topic is introduced by an account of a typical advanced case. There follow a half-dozen case reports, including autopsies, illustrating the ways in which this picture may be altered and even obscured by accompanying and sometimes independent conditions such as hypertensive disease, arteriosclerosis, congestive failure and glomerulonephritis.

The specificity of the glomerular lesions for diabetes has been questioned by some. The authors believe that, although there may be uncertainty on this score with respect to early or minimal lesions, the more severe forms, in which the majority of the glomeruli are involved with spherical hyaline bodies, are practically

pathognomonic of diabetic renal disease. Regarding the composition of these nodules, reference is made to the likelihood that, in view of their affinity for the periodic acid-Schiff reagent as reported by McManus, they contain a glycoprotein. The fact that the microaneurysms of the retina have similar staining reactions is noted, but the intriguing possibility raised by this fact, namely that the glomerular and the retinal lesions may have a common pathogenesis, is not given the attention it deserves.

Clear thinking concerning the underlying causes of the syndrome is evident in several places. For example, ". . . the majority of reports emphasize that the most frequent occurrence of diabetic glomerulosclerosis is among patients in the sixth and seventh decades of life, but so is the highest incidence of diabetes." In discussing the relationship between the duration of diabetes and the occurrence of the renal disorder, the authors emphasize, and document, the difficulty of determining onset and hence duration of diabetes. Refuting the idea that long duration is a necessary precursor, they cite the finding by Derow and Schlesinger (1949) of advanced intercapillary glomerulosclerosis in the right kidney of a diabetic woman only four years after the absence of such lesions had been established in the left kidney which had been removed for suspected tumor. In considering the relationship of the specific renal lesion to the degree of control of diabetes they state, quite properly, "The question of control is obviously related to the duration of diabetes because the longer the latter the more tedious and difficult the former."

For the most part the clinical data are similar to those of other investigators. The causes of death among autopsied patients are divided equally between uremia and cardiovascular disease, the two together accounting for 85 per cent of such deaths.

The chapter on laboratory aids in diagnosis is especially valuable in pointing out that in doubtful or complicated cases the finding of doubly refractile fat in the cells or casts of the urinary sediment is the best single indicator of diabetic glomerulosclerosis, provided glomerulonephritis can be excluded. None of the patients with generalized arteriosclerosis and hypertensive renal vascular disease showed this finding. The exclusion of glomerulonephritis may be difficult, but helpful criteria are given for this purpose.

Although recognizing that intercapillary glomerulosclerosis cannot be said to be entirely preventable at present, the authors are impressed by the recent studies of the Joslin group which demonstrate a significantly higher incidence of this and other vascular disorders in patients whose diabetes has been poorly controlled as compared with those under good control.

LIVER INJURY. *Transactions of the Tenth Conference, May 21-22, 1951. F. W. Hoffbauer, Editor. Pp. 320, $3.75. Josiah Macy, Jr. Foundation, New York, 1951.*

Volumes recording the transactions of the Macy Conferences have become known among scientific readers for their interesting presentation of factual data and speculations by outstanding investigators in the field under discussion. The conferences, and the volumes, owe much of their success to an informality which serves to break down barriers to exchange of ideas among the participants.

This volume on liver injury has the same quality of informality as its predecessors. It includes several sections, each composed of one or two opening presentations by able investigators and discussion by the other participants. Material on serum proteins and lipids is introduced by Roy H. Turner; lipotropic factors by Camillo Artom and David Cayer; experimental ischemia of the liver and hepatic coma by A. M. Rappaport; micro-anatomy of the hepatic vascular system by B. G. Maegraith; effect of insulin on the liver in normal and diabetic man by Sheila Sherlock, A. G. Bearn and B. Billing and liver disease in Jamaican children by Kenneth R. Hill.

Of particular interest to the reader who is concerned with diabetes are the studies of Sheila Sherlock and associates of the University of London on the effect of insulin on the production of glucose by the liver in 43 normal and 39 diabetic subjects. For these studies catherization of hepatic vein was employed. Sherlock's presentation forms the basis for considerable stimulating discussion of hepatic physiology in diabetes.

The 1952 Diabetes Detection Drive

The Committee on Detection and Education under the chairmanship of John A. Reed, M.D., conducted the 1952 Diabetes Detection Drive which was renewed during Diabetes Week, November 16-22. Organizational material on professional and lay levels was issued to Affiliate Societies, Committees on Diabetes and Secretaries of County and State Medical Societies as early as May 15. From then until the days immediately preceding Diabetes Week, a great number of pamphlets, posters, and leaflets; radio and television material; as well as testing kits, were made available to the Committees. Medical and professional journals were apprised of Detection Drive activities.

NATIONAL PUBLICITY

As the week of November 16-22 approached, the national publicity campaign arranged by the National Office of the Association was started.

On four consecutive days, at the opening of the annual program, the four major networks, totalling 1,300 stations, (ABC 326; CBS 214; MBS 562; NBC 194) allocated thirty minutes of their sustaining time to the Diabetes Detection Drive;—a record in introductory announcements for Diabetes Week.

Radio furnished such stars as Red Barber, Fred Allen, Tallulah Bankhead, Jimmy Durante, George Sanders, Meredith Wilson, and Lockwood Doty, the last a prominent radio announcer who is also a diabetic.

Distinguished diabetics who participated in many of these dramatic presentations were Bill (Swish) Nicholson, well-known big league ball player, Bill Talbert and Hamilton Richardson, Davis Cup teammates, Evelyn Lockhart, professional model, Mrs. Eva Saxl, and Mrs. Claire V. Rider, department store executive.

Ten of the leading network shows of the four radio systems carried spot announcements of the Drive and the Metropolitan Life Insurance Company made similar announcements during Diabetes Week on its many daily programs over 76 American and Canadian radio outlets.

In addition to such network coverage, 867 transcriptions were made available to Committees on Diabetes for use on their local radio stations and 1,338 scripts were furnished them for live dramatizations, interviews, and spot announcements.

In the field of television, similar publicity coverage was achieved. In addition to network television shows which featured diabetic celebrities as guests during the week, 52 sets of three slides each were prepared for local use in addition to the 21 slides prepared for the TV networks.

NEWSPAPER AND MAGAZINE COVERAGE

News stories were released almost daily by the Associated Press, the United Press, International News Service, and many other feature syndicates, starting November 9th. Their science and medical columnists enthusiastically cooperated by writing one or more columns apiece about diabetes and the necessity for its early detection during the week. As these writers' columns are supplied to thousands of papers throughout the country, our affiliates were advised to call the attention of their local papers to the availabiliy of these outstanding features.

A magazine and newspaper kit of educational material was prepared and distributed to all Committees on Diabetes and cooperating organizations before the drive, and many of these were used with unusual effectiveness in providing newspaper stories for local coverage.

Special effort was made this year to secure a wide magazine representation in Diabetes Week publicity. Articles appeared in the following publications: *Cosmopolitan, Glamour, Pageant, Parents' Magazine, Pathfinder, Today's Health, Variety,* etc. Many trade journals and company publications were also represented in this phase of the publicity.

PROFESSIONAL PUBLICATIONS

Special material was sent to professional magazines and State and County Medical Society Journals. Editorials and articles appeared prominently in the *Journal* of the American Medical Association, the *Journal* of the American Dietetic Association, the *Journal* of the American Pharmaceutical Association, *Postgraduate Medicine, Current Medical Digest, Medical Economics* and the *Southern Pharmaceutical Journal.*

Space only permits mentioning a few of the Medical Society Journals which called Diabetes Week to the attention of their members. Articles appeared in the

New York State *Journal of Medicine* and the *Newsletter* of the Medical Society of the State of New York, the *Bulletin* of Orleans Parish Medical Society, King County Medical Society *Bulletin* (Seattle, Ore.), the *Bulletin* of the Medical Society of Erie County (New York), the *Quincy Medical Bulletin* (Adams County, Ill.), and the *Bulletin* of Oklahoma County Medical Society.

The *Journal* of the Michigan State Medical Society dedicated its October issue to diabetes and the Detection Drive with ten articles on the subject.

Articles by members of the Association appeared in many trade journals, company publications and labor magazines. Widely distributed were "Working with Diabetes," by Frank N. Allan, M.D. and "Diabetes—A Detective Story," by John A. Reed, M.D.

ENDORSEMENTS

Both the American Medical Association and the American Pharmaceutical Association previously had twice endorsed the Diabetes Detection Drive. This year the Bureau of Medicine and Surgery of the Navy Department made a diabetic survey a standard service of the U. S. Navy's occupational program for Civil Service employees.

Previous endorsements that may be mentioned are those of the American Federation of Labor and the Congress of Industrial Organizations and The Advertising Council, Inc. Special endorsements have also been received from the American Dietetic Association and the American Nurses' Association.

Bill Talbert, former captain of the U. S. Davis Cup team who has generously lent his efforts to previous drives, travelled from Boston to Seattle during this Diabetes Week playing exhibition tennis matches in ten cities in ten days.

SUCCESSFUL MEETINGS

The Philadelphia Metabolic Association held a successful meeting in the auditorium of the Philadelphia Medical Society on November 17th. W. C. Stadie, M.D., of the University of Pennsylvania, outlined current advances in diabetes research and Henry D. Cornmann III, M.D. answered questions on diabetes asked by the audience.

Once again, the New England Diabetes Association held a Diabetes Fair at Horticultural Hall in Boston. This exposition provided facilities for urine and blood testing and chest x-rays; motion pictures were shown and ten exhibits on as many different phases of diabetes —its detection and control, were assembled by voluntarily cooperating groups.

In Toronto, over 1,700 visitors attended the meeting of the Diabetes Association of Ontario meeting during Diabetes Week; 500 individuals had to be accomodated at an overflow meeting at another hall at the University of Toronto and over 100 persons joined the Ontario Association.

At Easton, Pa., the Lay Society of the Lehigh Valley Diabetes Association organized their Diabetes Week meeting around a program emphasizing the role of diabetes in industry and business.

ST. LOUIS USED DREYPAK DEVICE

In St. Louis, Mo., over 100,000 Dreypak kits were distributed through druggists by the St. Louis Diabetes Association, repeating the use of this comparatively new and effective means of mass testing. Earlier experiences with the Dreypak method in mass screening is described by Doctors Olmsted, Drey, Agress, and Roberts in this issue of DIABETES (see page 37).

The Far East Command of the U. S. Army participated in Diabetes Week by setting up clinics in Japan and Okinawa for the testing of civilian personnel and military dependents.

The Medical Welfare Department of the Republic Aircraft Corporation in Farmingdale, Long Island, cooperated in the Diabetes Detection Drive by setting up a screening program for its 23,000 employees.

In New York City, several screening centers were arranged to handle the huge population of that city and the drive was formally opened by Mayor Impellitteri and Henry G. Jacobi, M.D., then President of the New York Diabetes Association, at City Hall.

RESULTS BEING EVALUATED

The above highlights are only a few of the nationwide activities performed during Diabetes Week. Reports are still being received from Committees on Diabetes and tabulated results continue to be compiled in the National Office.

The Committee on Detection and Education, John A. Reed, M.D., Chairman, has offered the Committee's appreciation and thanks to the many Association members on Committees on Diabetes Detection of Affiliate Organizations, and on Committees on Diabetes in their County and State Medical Societies who have done so much to make the year's program an outstanding success.

ASSOCIATION NEWS

SUCCESS OF FIRST POSTGRADUATE COURSE ASSURED

From the standpoint of registrations, at least, the success of the Postgraduate Course in Diabetes and Metabolic Problems to be held at the University of Toronto, January 19-21, has been guaranteed. The response has been beyond expectations and, at the time this goes to press, over 240 applications for the course have been received. A maximum number of 100 registrations was previously established, and although this has been extended by more than fifty per cent, it has been necessary to reject a great many applications. As mentioned in preliminary announcements, every effort has been made to register all members. To date no member has been unable to obtain admission.

There will be a report on the postgraduate course in the next issue and many of the papers delivered at the Toronto meeting will be published in future issues of DIABETES.

THIRTEENTH ANNUAL MEETING

As previously announced, the next Annual Meeting of the AMERICAN DIABETES ASSOCIATION will be held on May 30-31, 1953 at New York City. The meeting will precede, as is customary, the Annual Session of the American Medical Association, June 1-5. On Saturday afternoon, May 30, there will be a joint meeting of the ADA and The Endocrine Society at ADA headquarters, Hotel Commodore.

THE BANTING MEMORIAL LECTURE

The Banting Memorial Lecture to be given at the joint session will be delivered by Shields Warren, M.D., of Boston, who has chosen as his subject: "An Interpretation of Diabetes in the Light of its Pathology".

Doctor Warren, well known to everyone interested in diabetes and allied subjects, is co-author of *The Pathology of Diabetes Mellitus,* and is Professor of Pathology at the New England Deaconess Hospital. He holds a great many other important appointments and was formerly Director of the Division of Biology and Medicine, United States Atomic Energy Commission, and Chairman of the Scientific Advisory Board, Armed Forces Institute of Pathology.

REQUEST FOR PAPERS

Henry B. Mulholland, M.D., Second Vice President and Chairman of the Committee on Scientific Programs of the Association, issues a cordial invitation to all physicians and other scientists to submit for consideration abstracts of papers which they would like to present at the Scientific Sessions.

STATEMENT ON EMPLOYMENT

A limited number of printed leaflets entitled *Employment of Diabetics,* based on the Statement on Employment as approved by the Council at its last meeting, are available. The leaflet has not been prepared for distribution to diabetics, but rather to medical directors of industry and labor organizations, as well as company personnel managers. Members interested in the problems of employment of diabetics, especially those participating in the activities of Affiliate Associations and Committees on Diabetes of County and State Medical Societies will find this particularly helpful in discussing the problem with industry.

The statement in full was published in Volume 1, No. 4 of DIABETES.

DIABETIC PHYSICIANS ACCEPTED FOR MILITARY SERVICE

The Department of Defense has altered the physical standards for commissioning in the medical, dental and veterinary corps of the armed forces. A new directive signed by Assistant Defense Secretary Anna M. Rosenberg, Chief of Personnel and Manpower, calls for a review of all cases previously found physically disqualified because of "absence of parts, static orthopedic defects, the requirement of maintenance medication, the statis sequelae of arrested acute and chronic disease processes, defective visual and auditory acuity, and some active processes relatively asymptomatic or of which the symptoms are not essentially disabling. In general, those with statis impairment and those with chronic progressive or recurrent disease, if asymptomatic or relatively so, are considered to be acceptable for service." It is understood that diabetic physicians could qualify for service. Each case, however, will be considered individually.

PUBLIC HEALTH SERVICE GRANTS

The National Institute of Arthritis and Metabolic Diseases awarded $666,893 for 67 research grants and $77,696 for 22 research fellowships in June, 1952. These sums were approved by the Surgeon General of the Public Health Service following recommendations of reviewing consultants.

A record sum of $14,071,133 for research grants will be considered by the advisory councils of the National Institutes of Health, and the sum of $1,253,853 covering 121 projects will be reviewed by the advisory council for the National Institute of Arthritis and Metabolic Diseases.

NEW RESEARCH UNIT AT CANCER INSTITUTE

The National Cancer Institute has established a new branch in research medicine which will be headed by Roy Hertz, M.D., who was formerly in charge of the Endocrinology Unit at NCI.

The establishment of this branch in research medicine and another one in clinical medicine and surgery is one of the many administrative preparations being made before the opening of the 500-bed Clinical Center at the National Institutes of Health this spring.

BINDERS FOR DIABETES

Response to the previous announcements of the availability of binders for DIABETES has been below expectation. Inasmuch as the price of $2.00 each was based on at least 100 orders it would be appreciated if members and subscribers would place their orders just as soon as possible. The insert binder is sturdy, attractive and will hold six issues, forming one volume.

Further, many physicians, as well as librarians, prefer to have their issues in permanent buckram binding. To accommodate them, we can provide *additional* sets with library-type binding at a cost of $9.00. This includes the six copies of DIABETES, as well as the binding.

Individuals and libraries thereby will be able to have their single copies available for reference and may secure a bound set for permanent use.

BACK COPIES OF DIABETES ABSTRACTS NEEDED

Although *Diabetes Abstracts* have not been printed since 1951, there is still considerable demand for back issues of this valuable publication. We are in short supply of the following issues: Volume III, No. 2; Volume IV, Nos. 2, 3 and 4; Volume V, No. 4; Volume VI, Nos. 2, 3 and 4; Volume VII, Nos. 1, 3 and 4; Volume VIII, Nos. 1 and 2.

It would be appreciated if members and other readers who have duplicate copies or no longer need the above issues would send them to the National Office.

CONGRESS ON DIABETES AT VALS LES BAINS, FRANCE

Last September 14-18, a Congress on Diabetes was held at Vals les Bains, France, under the presidency of the French Minister of Public Health, M. Ribeyre.

According to the report of the International Diabetes Federation, practically all prominent French diabetes specialists took part in the Meeting and presented able discussions, most of which were devoted to social problems in connection with diabetes. Papers read to the Congress have been published in the *Rapports de la Societe Medicale de Vals les Bains,* Imprimerie Habaurit, 1952.

Plans for a diabetic clinic to be erected in Vals les Bains were shown to the members.

Dr. R. D. Lawrence, President of the I. D. F., was unable to attend, but the Federation was represented by its Secretary-Treasurer, Dr. F. Gerritzen.